In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: August 28, 2023

URIEL ZAMORA and EDNA FRIAS, father and mother and natural guardians of minor, A.Z.,	*	PUBLISHED
Petitioners,	*	No. 19-1718V
v.	*	Special Master Nora Beth Dorsey
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Entitlement; Influenza ("Flu") Vaccine; Hepatitis A Vaccine; Opsoclonus Myoclonus Syndrome ("OMS");
Respondent.	*	Opsoclonus Myoclonus Ataxia ("OMA").

Jeffrey S. Pop, Jeffrey S. Pop & Associates, Beverly Hills, CA, for Petitioner.
James Vincent Lopez, U.S. Department of Justice, Washington, DC, for Respondent.

RULING ON ENTITLEMENT[1]

I. INTRODUCTION

On November 5, 2019, Uriel Zamora and Edna Frias, father and mother and natural guardians of their minor child, A.Z., ("Petitioners") filed a petition for compensation under the National Vaccine Injury Compensation Program ("Vaccine Act" or "the Program"), 42 U.S.C. §

[1] Because this Ruling contains a reasoned explanation for the action in this case, the undersigned is required to post it on the United States Court of Federal Claims' website and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). **This means the Ruling will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), Petitioners have 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, the undersigned agrees that the identified material fits within this definition, the undersigned will redact such material from public access.

300aa-10 et seq. (2018).[2] Petitioners alleged that as a result of receiving the influenza ("flu") vaccine on November 30, 2016 and the hepatitis A vaccine on December 14, 2016, A.Z. developed ataxia and opsoclonus myoclonus syndrome ("OMS"), also known as opsoclonus myoclonus ataxia ("OMA").[3] Petition at Preamble (ECF No. 1). Respondent argued against compensation, stating that "this case is not appropriate for compensation under the [Vaccine] Act." Respondent's Report ("Resp. Rept.") at 1 (ECF No. 30) (emphasis omitted).

After carefully analyzing and weighing the evidence presented in this case in accordance with the applicable legal standards, the undersigned finds that Petitioners have proven by preponderant evidence that the flu vaccination caused A.Z.'s OMS. Thus, Petitioners have satisfied their burden of proof under Althen v. Secretary of Health & Human Services, 418 F.3d 1274, 1280 (Fed. Cir. 2005). Accordingly, Petitioners are entitled to compensation.

II. ISSUES TO BE DECIDED

Diagnosis is not at issue. Joint Submission, filed July 18, 2022, at 1 (ECF No. 84). The parties agree that the diagnosis of OMS is not in dispute. Id. Additionally, the parties stipulate that A.Z. received the flu vaccine on November 30, 2016 and the hepatitis A vaccine on December 14, 2016. Id.

The first issue is whether Petitioners have met their burden to establish that a vaccination caused A.Z.'s OMS. Joint Submission at 1. Petitioners assert that they have met their burden under all three Althen prongs. Petitioner's Brief in Support of Finding for Entitlement ("Pet. Br."), filed July 18, 2022, at 2, 29-50 (ECF No. 87). Respondent disagrees and argues that Petitioners failed to demonstrate by preponderant evidence that the flu or hepatitis A vaccines caused A.Z.'s OMS. Resp. Response to Pet. Br. ("Resp. Br."), filed Oct. 17, 2022, at 2, 31-43 (ECF No. 92).

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to -34 (2018) ("Vaccine Act" or "the Act"). All citations in this Ruling to individual sections of the Vaccine Act are to 42 U.S.C.A. § 300aa.

[3] There are multiple acronyms for the condition at issue here. See Petitioner's Exhibit ("Pet. Ex.") 63 at 2 (Thomas Rossor et al., Diagnosis and Management of Opsoclonus-Myoclonus-Ataxia Syndrome in Children, 9 Neurology: Neuroimmunology & Neuroinflammation e1 153 (2022). OMS has also been referred to as OMA, myoclonic encephalopathy, opso-myoclonus, dancing eye syndrome, and Kinsbourne syndrome. Pet. Ex. 39 at 1 (Elizabeth D. Tate et al., Neuroepidemiologic Trends in 105 US Cases of Pediatric Opsoclonus-Myoclonus Syndrome, 22 J. Pediatric Oncology Nursing 8 (2005). This is also cited by Respondent. Resp. Ex. B, Tab 4); Respondent's ("Resp.") Ex. B, Tab 3 at 1 (K. Ki Pang et al., A Prospective Study of the Presentation and Management of Dancing Eye Syndrome/Opsoclonus-Myoclonus Syndrome in the United Kingdom, 14 Eur. J. Pediatric Neurology 156 (2010)). For clarity, the undersigned will use the abbreviation OMS throughout this Ruling.

The second issue relates to whether alternative factors unrelated to vaccination caused A.Z.'s condition. Joint Submission at 1. If Petitioners meet their burden on causation, the remaining question is whether Respondent has met his burden to show that factors unrelated to the vaccinations caused A.Z.'s OMS.[4] Id.

III. BACKGROUND

A. Medical Terminology

OMS is a "rare, autoimmune neurological disorder" mainly occurring in young children.[5] Pet. Exhibit ("Ex.") 39 at 1; see also Pet. Ex. 35 at 1;[6] Pet. Ex. 56 at 1.[7] While rare, it is "the most common paraneoplastic neurologic syndrome in children. A paraneoplastic syndrome is a disease or symptom that is the consequence of the presence of a malignancy in the body but is not due to the local presence of the tumor or its metastases." Pet. Ex. 27 at 4.[8] Cases that are not associated with neuroblastomas[9] are thought to be "parainfectious or idiopathic."[10] Id. A

[4] A petitioner is not entitled to compensation if Respondent can prove, by a preponderance of the evidence, that the vaccinee's injury is "due to factors unrelated to the administration of the vaccine." § 13(a)(1)(B).

[5] OMS also occurs in adults; however, there is evidence to suggest that the factors relevant to etiology are different for pediatric and adult OMS cases. See Pet. Ex. 31 at 20 (Michael R. Pranzatelli, The Immunopharmacology of the Opsoclonus-Myoclonus Syndrome, 19 Clinical Neuropharmacology 1 (1996)).

[6] Michael R. Pranzatelli et al., Demographic, Clinical, and Immunologic Features of 389 Children with Opsoclonus-Myoclonus Syndrome: A Cross-Sectional Study, 8 Frontiers Neurology 468 (2017). This is also cited by Respondent. Resp. Ex. B, Tab 7.

[7] Yvonne Shea, Opsoclonus Myoclonus Syndrome, Autoimmune Registry, https://www.autoimmuneregistry.org/opsoclonus-myoclonus-syndrome (last visited July 3, 2023).

[8] Thomas E. Hermon & Marilyn J. Siegel, Ataxia Without Opsoclonus: Right Lumbar Sympathetic Trunk Neuroblastoma, 48 Clinical Pediatrics 336 (2009).

[9] Neuroblastoma is a "sarcoma consisting of malignant neuroblasts, usually arising in the autonomic nervous system (sympathicoblastoma) or in the adrenal medulla; it is considered a type of neuroepithelial tumor and affects mostly infants and children up to 10 years of age." Neuroblastoma, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition? id=33659 (last visited June 27, 2023). Sarcoma refers to "any of a group of tumors usually arising from connective tissue, . . . some of epithelial origin; most are malignant." Sarcoma, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=44640 (last visited June 27, 2023).

[10] For more detailed information about OMS, see Pet. Ex. 35.

"paraneoplastic[11] association" has been "proven in [] 50% of OMS cases." Pet. Ex. 35 at 19; see also Pet. Ex. 39 at 1, 3 (noting a neuroblastoma is found in about half of the cases).

"Inflammation in the neurological system causes the disorder." Pet. Ex. 56 at 1. It is characterized by "opsoclonus[12] (fast, multidirectional, conjugate eye movements), a jerky ataxia[13] sometimes with a myoclonic component,[14] marked irritability and/or sleep disturbance and, in some cases, an accompanying neuroblastoma." Resp. Ex. B, Tab 3 at 1. Other characteristics include falling, tremors, drooling, inability or refusal to walk or sit, speech problems, decreased muscle tone, and behavioral problems. Pet. Ex. 39 at 1, 3, 8 fig.4. Non-neurological antecedent symptoms include "irritability, upper respiratory symptoms, ear infections, fever, lethargy, vomiting, and diarrhea." Id. at 3. Diagnosing OMS is difficult and often results in a delayed diagnosis. See Pet. Ex. 35 at 18; Pet. Ex. 25 at 4.[15] It is commonly misdiagnosed as acute cerebellar ataxia or Guillain-Barré syndrome ("GBS"). Pet. Ex. 39 at 3; Resp. Ex. B, Tab 3 at 2.

"[T]he pathophysiology of [the] condition remains unknown although there is evidence of immune dysregulation." Resp. Ex. B, Tab 3 at 4; see also Resp. Ex. B, Tab 5 at 4.[16] The cause of the OMS is thought to be an autoimmune response, and several mechanistic processes have been suggested. See Pet. Ex. 29 (suggesting the etiology of OMS is autoimmune in

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[11] Paraneoplastic means "pertaining to changes produced in tissue remote from a tumor or its metastases." Paraneoplastic, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=36883 (last visited June 27, 2023).

[12] Opsoclonus is "a condition characterized by nonrhythmic horizontal and vertical oscillations of the eyes, observed in various disorders of the brainstem or cerebellum." Opsoclonus, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=35338 (last visited June 27, 2023).

[13] Ataxia is the "failure of muscular coordination; irregularity of muscular action." Ataxia, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=4630 (last visited June 27, 2023). Ataxia is often used to describe a gait abnormality. See Pet. Ex. 56 at 2; Pet. Ex. 35 at 2, 20.

[14] A myoclonic component refers to "shock like contractions of a portion of a muscle, an entire muscle, or a group of muscles, restricted to one area of the body or appearing synchronously or asynchronously in several areas. It may be part of a disease process . . . or be a normal physiologic response." Myoclonus, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=32802 (last visited June 27, 2023).

[15] Jay Desai & Wendy G. Mitchell, Acute Cerebellar Ataxia, Acute Cerebellitis, and Opsoclonus-Myoclonus Syndrome, 27 J. Child Neurology 1482 (2012).

[16] Armine Galstyan et al., Opsoclonus-Myoclonus Syndrome: A New Era of Improved Prognosis?, 72 Pediatric Neurology 65 (2017).

nature).[17] "OMS typically occurs with tumors (neuroblastomas) or after a viral or bacterial infection. The immune reaction to the tumor or infection makes the body attack the nervous system. In some cases, the cause is unknown." Pet. Ex. 56 at 1. "In children without a demonstrated tumor [often neuroblastoma], a viral etiology is inferred, often based on a 'viral prodrome' consisting of upper respiratory or gastrointestinal symptomatology." Pet. Ex. 39 at 1-2. Accordingly, two subtypes of OMS have been recognized based on suspected etiology—post-infectious and paraneoplastic (neuroblastoma). Pet. Ex. 20 at 8.

B. Procedural History

Petitioners filed a petition on November 5, 2019, alleging that the flu vaccine administered on November 30, 2016 and the hepatitis A vaccine administered on December 14, 2016 caused in fact A.Z.'s OMS/OMA. Petition at Preamble. On November 12, 2019, Petitioners filed medical records, an affidavit, an expert report by Dr. Marcel Kinsbourne, and supporting medical literature. Pet. Exs. 1-41. On February 11, 2020, Respondent filed a status report indicating he would be contesting entitlement, and on April 7, 2020, Petitioner filed updated medical records. Resp. Status Rept., filed Feb. 11, 2020 (ECF No. 18), Pet. Ex. 42. On June 23, 2020, Respondent filed his Rule 4(c) Report stating Petitioners were not entitled to compensation because they "presented insufficient evidence of vaccine causation under Althen." Resp. Rept. at 18. The same day, Respondent filed an expert report by Dr. Hayley Gans. Resp. Ex. A. On August 24, 2020, Petitioners filed a video showing A.Z.'s gait. Pet. Ex. 43.

Petitioners filed a supplemental expert report from Dr. Kinsbourne on September 22, 2020, and Respondent filed a supplemental expert report from Dr. Gans on January 25, 2021. Pet. Ex. 45; Resp. Ex. C. From April 2021 to March 2022, the parties filed three more supplemental expert reports from Dr. Kinsbourne and Dr. Gans. Pet. Exs. 50, 53, 57; Resp. Exs. D-F. Updated medical records were also filed throughout this time. Pet. Exs. 51-52.

In a joint status report filed on March 16, 2022, the parties indicated the record was complete, that they agreed to resolve the issue of entitlement through a ruling on the record, and they proposed a briefing schedule. Joint Status Rept., filed Mar. 16, 2023 (ECF No. 78); see also Order dated Mar. 17, 2022 (ECF No. 79).

On July 18, 2022, Petitioners filed medical records and additional medical literature. Pet. Ex. 58-63. Petitioners filed their motion for a ruling on the record on July 18, 2022, and Respondent filed a response on October 17, 2022. Pet. Br.; Resp. Br. Petitioners filed a reply brief on January 17, 2023. Pet. Reply to Resp. Br. ("Pet. Reply"), filed Jan. 17, 2023 (ECF No. 95).

This matter is now ripe for adjudication.

[17] M. Kinsbourne, Myoclonic Encephalopathy of Infants, 25 J. Neurology Neurosurgery & Psychiatry 271 (1962).

C. Factual Background

1. Medical History

a. Pre-Vaccination Medical History

A.Z. was born on April 30, 2015. Pet. Ex. 7 at 30-31. He was born full term and weighed 8 pounds, 15 ounces. Id. at 11-12. A.Z. had a normal newborn screening except for a suspected heart murmur. Id. at 35, 37. A.Z. and his mother were discharged home with instructions to follow up with the pediatrician and a pediatric cardiologist for the heart murmur. Id. at 12. Jaundice precautions were also noted. Id.

A.Z. had an initial newborn exam and well-child visit on May 4, 2015 at the Babies and Children's Clinic. Pet. Ex. 5 at 2. It was noted that there were no complications during the birth, but that A.Z. had a heart murmur that was to be addressed. Id. On physical examination of four-day-old A.Z., a systolic heart murmur and slight jaundice were documented. Id. at 3-4. A.Z. was referred to cardiology.[18] Id. at 4.

On June 23, 2015, A.Z. presented to his primary care provider ("PCP") with a skin mass at or near the belly button. Pet. Ex. 5 at 11. The mass was described as "raised" but had been "essentially asymptomatic" since it was first noticed the day before. Id. The assessment was an unspecified umbilical cord complication, and he was referred to a surgeon for evaluation. Id. at 12. At his June 30, 2015 well-child visit, A.Z. presented with constipation. Id. at 13-14.

A.Z. received all routine childhood vaccinations[19] and had a relatively healthy infancy but was evaluated several times for upper respiratory infections ("URIs") and ear infections. See Pet. Ex. 5 at 15-32; Pet. Ex. 10 at 20-26. For example, in August 2015, A.Z. presented with a cough and chest congestion. Pet. Ex. 5 at 17. A "rash over different parts of [his] body" was observed on examination. Id. at 19. The assessment was an acute URI, atopic dermatitis, and gastroesophageal reflux disease ("GERD"). Id. And in November and December 2015, A.Z. again presented with a cough and congestion as well as a fever. Id. at 24-34. The assessments were acute bronchiolitis, acute otitis media (ear infection), acute pharyngitis, flu-like symptoms, and anemia. Id. at 32. In January 2016, A.Z. had four sick visits with Dr. Luis A. Rodriguez at the Children's Clinic for fever, cough, and diarrhea. Pet. Ex. 10 at 23-26. A.Z. tested positive for respiratory syncytial virus ("RSV"). Pet. Ex. 7 at 70.

At his one-year-old wellness visit on May 5, 2016, there were no concerns, and A.Z. had normal growth/development and a normal examination. Pet. Ex. 5 at 35-38. Petitioners reported

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[18] A.Z. was referred to Dr. Jyoti Gupta for cardiology. Pet. Ex. 5 at 4. Besides the initial echocardiogram on May 1, 2015, Dr. Gupta's records were not filed. See Pet. Ex. 7 at 37. Future primary care examinations did not reveal the murmur.

[19] A.Z. received the varicella, hepatitis A, and measles-mumps-rubella ("MMR") vaccines on May 5, 2016. Pet. Ex. 5 at 37. A.Z. received the haemophilus B conjugate ("ActHIB") and pneumococcal conjugate 13-valent vaccines on May 13, 2016. Id. at 39.

A.Z. was able to "take a few steps alone, reach for objects with a precise pincer grasp, use a cup, help [] to feed self . . . imitate vocalizations, [and able] to say a couple words." Id. at 35.

On May 18, 2016, A.Z. had a sick visit with Dr. Rodriguez for a rash and a cough. Pet. Ex. 10 at 22. On August 31, 2016, A.Z. had a sick visit with Dr. Rodriguez for a fever and a cough. Id. at 21. And on November 2, 2016, A.Z. returned to Dr. Rodriguez with a fever but "no respiratory symptoms [and] no gastrointestinal symptoms" were noted. Id. at 20; see also Pet. Ex. 58 at 3. Labs taken during that visit were insignificant. Pet. Ex. 58 at 3. On November 21, 2016, A.Z. presented to Pediatrics Associates at Ridge because he had a "runny nose . . . for 3-4 days and congestion cough with phlegm." Pet. Ex. 6 at 14. The diagnoses were acute bilateral otitis media, acute bronchiolitis, allergic rhinitis, and constipation. Id. at 16. He was prescribed antibiotics. Id. at 16-17.

A.Z. had his 18-month well-child checkup on November 23, 2016 with Dr. Hildegardo Costa. Pet. Ex. 6 at 6-13. At this visit, he had no fever, vomiting, or diarrhea, but his "coughing seem[ed] to be worsening." Id. at 6-7. Growth and development were normal. See id. at 6-13. It was noted that he was still taking antibiotics and was instructed to continue them as well as to start Orapred. Id. at 6, 11. Dr. Costa noted that A.Z.'s 18-month vaccines were "pending due to illness" and that he could receive them when he was well again. Id. at 11. The annual flu vaccine was recommended. Id.

b. Vaccination and Post-Vaccination Medical History

On November 30, 2016, A.Z. returned to Dr. Costa for a follow-up for his acute bronchiolitis and ear infection. Pet. Ex. 6 at 1-5. A.Z. still had "an occasional cough with phle[g]m and runny nose with clear mucus [since the] last visit." Id. at 2. He had completed the prescribed course of antibiotics and had no fever. Id. Dr. Costa noted A.Z.'s cough was "much less" and there was no wheezing. Id. On physical examination there was mild congestion of the nose and dull tympanic membranes. Id. at 3. No rash was present. Id. At this visit, A.Z. received the flu vaccine at 19 months old. Id. at 4; Pet. Ex. 2 at 1-2.

On December 14, 2016, A.Z. returned to Dr. Rodriguez at the Children's Clinic for a well-child assessment. Pet. Ex. 58 at 4. At this visit, A.Z. received his second dose of the hepatitis A vaccine. Id.; Pet. Ex. 3 at 1; Pet. Ex. 10 at 18. There were no concerns documented at this visit. Pet. Ex. 10 at 16-19; Pet. Ex. 58 at 4.

A.Z. was taken to Dr. Rodriguez on January 7, 2017 because his mother was "concerned about [A.Z.] shaking for [four] days." Pet. Ex. 58 at 5. He was also eating less and had a cough with phlegm. Id.; see also Pet. Ex. 10 at 15. The history indicated that A.Z.'s gait had been "occasional[ly] unstable" for the past four days. Pet. Ex. 58 at 5. He would be "walking and suddenly stop [] and he seem[ed] uncertain in continuing walking, slightly shaky." Id. It was reported that this happened three to four times per day, each lasting less than one minute. Id. There was no associated fever, vomiting, or loss of consciousness. Id. Past history noted that A.Z. started walking at 15 months old, was unstable running then, but other developmental skills were appropriate for his age. Id. Regarding his four-day nasal congestion, Dr. Rodriguez recorded that A.Z. had a "wet cough" and he was "[t]reated once with medication from Mexico

[four] days ago." Id. On examination, there was "occasional rhonchi" and Dr. Rodriguez observed that A.Z. walked "with slight open legs." Id. The diagnoses were "[u]nsteady gait, [v]ery mild motor delay, [and] [b]ronchitis." Id. A referral was made for a neurology consultation. Id.

Pediatrician Dr. Marco Lopez evaluated A.Z. on January 16, 2017 for "tremors" that began three weeks prior. Pet. Ex. 15 at 2. A.Z.'s father characterized them as "episodes" that were "constant" and of "moderate intensity." Id. He described the episodes as "shaking of arms and legs lasting few minutes." Id. He also described that A.Z. would "go down to the ground/floor to lie down, as if he [was] afraid to fall. After the episode he [would] get [] up and [was] able to walk around." Id. Associated symptoms included unstable walking. Id. Dr. Lopez assessed A.Z. with having seizures and referred him to a neurologist. Id. at 4.

A.Z. was hospitalized at Rio Grande Hospital from January 18-20, 2017. Pet. Ex. 7 at 90, 119. On January 18, 2017, A.Z. presented to the emergency department ("ED") for "shaking, tremors, and unbalance gait for few days" that was "gradually worsening." Id. at 111. Petitioners denied fever or irritability. Id. The primary impression was ataxia. Id. at 114.

A computerized tomography ("CT") scan was performed upon admission and was normal. Pet. Ex. 7 at 116-17. An electroencephalography ("EEG") was done the following morning while A.Z. was still sleeping. Id. at 116. The EEG was "within normal limits" for his age, but he had "intermittent body jerks associated with some irregular slow and sharp waves of [one] to [two] second duration." Id. at 139. The clinical interpretation was "suspicious of mild cerebral dysfunction compatible with the possibility of atypical benign myoclonic epilepsy" and further workup was recommended. Id. at 140. Laboratory studies, specifically the respiratory virus panel was positive for coronavirus.[20] Id. at 116. Id. Magnetic resonance imaging ("MRI") of the brain was ordered.[21] Id.

Attending physician Dr. Mahwish Nasir saw A.Z. on January 19, 2017. Pet. Ex. 7 at 108. History indicated A.Z. had "1.5 mo[nths] of abnormal movements . . . characterized by shaking/trembling movements of the upper and lower extremities" that occurred while walking or while sitting that "usually self-resolve[d] after minutes to a half hour." Id. Petitioners reported A.Z. had "waking episodes" at night, with "back arching, anger, dilated pupils, elevated heart rate, [and] appear[ing] to be awake but not interactive during the episodes." Id. Petitioners denied fever and decreased activity. Id. Physical examination showed no sensory deficits, mild hand trembling, but the ability to suppress with pressure. Id. at 110. A.Z. refused to walk during examination but Dr. Nasir saw a video of A.Z. waking at home that "demonstrated wide based

[20] Coronavirus is any virus belonging to the family Coronaviridae and causes "respiratory disease and possibly gastroenteritis in humans, and hepatitis, gastroenteritis, encephalitis, and respiratory disease in other animals." Coronavirus, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=11204 (last visited Aug. 7, 2023).

[21] An MRI of the brain was not completed during A.Z.'s hospitalization due to malfunctioning equipment. Pet. Ex. 8 at 5.

gait generalized twitching/trembling movements of legs and at times upper extremities." Id. Dr. Nasir's assessment was a myoclonic disorder, and he suspected myoclonic epilepsy. Id.

Also on January 19, 2017, A.Z. had a consultation with neurologist Dr. Leonardo Garcia. Pet. Ex. 7 at 115. History indicated that according to Petitioners, A.Z. "had tremors always, which had been getting worse in the past week to the point that he ha[d] difficulty in holding up and standing." Id. It was also reported that for two weeks, he had been "waking from a relaxed sleep into a rage anger or anxiety episodes. He screamed, threw himself back, confused with his eyes not fixing, and with extreme rage. . . . At times, his eyes have rolled back during these attacks." Id. He noted there was "no history of head trauma, no meningitis or encephalitis, no seizures, no allergies, no visual problems, [and] no serious medical illnesses." Id. Dr. Garcia found A.Z. to be "very combative." Id. at 116. Dr. Garcia's impression was that A.Z. was a "clumsy hyperactive child with short temper" making it difficult to be sure if he had ataxia. Id. at 116, 118. He also found no evidence of myoclonus. Id. The possibility of a neurometabolic disorder was considered. Id. at 118. A.Z. was discharged from the hospital on January 20, 2017 and ordered to follow up with his PCP (Dr. Rodriguez) and with Dr. Garcia (neurologist). Id. at 90.

On January 23, 2017, A.Z. had a post-hospitalization appointment with Dr. Rodriguez. Pet. Ex. 58 at 6. History indicated A.Z. "continued with moderate unsteady gait, not worse, not better since hospitalization. No fever." Id. at 6. Dr. Rodriguez noted "post-infection, tumor, [demyelination], and metabolic" under the ataxia diagnosis. Id.

A.Z. had a post-hospitalization appointment with Dr. Garcia on January 24, 2017. Pet. Ex. 8 at 5. History indicated he previously evaluated A.Z. during his recent hospitalization for "apparent ataxia for several months, probably worsening." Id. The assessment included progressive cerebellar ataxia, clumsiness, and hyperkinetic syndrome with developmental delay. Id. at 6.

A.Z. returned to Dr. Rodriguez on January 25, 2017 with "no significant change in status." Pet. Ex. 58 at 7. A.Z. had "very unstable gait, with mild truncal ataxia and of arms when trying to reach something, no nystagmus, no more jerking of body, no fever." Id. The diagnoses were ataxia, unsteady gait, and history of myoclonus. Id. Dr. Rodriguez was "[c]oncerned about brain lesion and neuroblastoma." Id.

On January 31, 2017, A.Z. returned to Dr. Garcia to review imaging studies performed on January 27. Pet. Ex. 8 at 7. The MRI of the brain was normal.[22] Id. Dr. Garcia noted that at his initial evaluation of A.Z. during his hospitalization, the "[p]ossibility of benign myoclonic epilepsy [] was suspected, [but] no[t] conclusive." Id. At this visit, A.Z. had "somewhat improved since last visit. Still ataxic. Not sure if having myoclonic jerks intermittently." Id. The assessment was progressive cerebellar ataxia but that A.Z. "ha[d] been stable or better since last visit." Id. at 8. "Cause still unknown" was documented. Id. Dr. Garcia intended to investigate myoclonic epilepsy. Id. Clumsiness, hyperkinetic syndrome with developmental

[22] A CT scan of the abdomen/pelvis was normal. Pet. Ex. 8 at 7. A CT of the chest showed pneumonia and atelectasis. Id.

delay, and cerebellar ataxia were also noted in the assessment. Id. Dr. Garcia ordered A.Z. to undergo a CCTV/video EEG[23] for further evaluation. Id.

The CCTV/video EEG was performed on February 8, 2017. Pet. Ex. 8 at 10-11. The clinical interpretation was "mild[ly] abnormal" showing intermittent slow activity observed in the occipital region during wakefulness and sleep; posterior dominant activity, which was considered slow for A.Z.'s age; and occasional epileptic activity bilateral and independent of the occipital region during sleep, often associated with slow activity. Id. at 11. The testing was "indicative of seizure tendency of occipital origin, [and] cortical dysfunction affecting occipital region." Id. The results were similar to those of the EEG done while A.Z. was hospitalized on January 19, 2017. Id.

On February 13, 2017, A.Z. presented to Dr. Rodriguez for three days of congestion and one day of fever. Pet. Ex. 10 at 12; see also Pet. Ex. 58 at 8.

A.Z. returned to Dr. Garcia to review the CCTV/video EEG on February 14. Pet. Ex. 8 at 12. On physical examination, A.Z. had "some drooling." Id. at 13. He had "been stable but not better since last visit." Id. The suspected myoclonic epilepsy was ruled out because the "EEG changes, despite abnormal, [were] not typical for the condition." Id. Diagnosis remained persistent cerebellar ataxia. Id. Dr. Garcia again documented that the cause was "still unknown" but added that the "[p]ossibility of postimmunization reaction is strongly considered." Id. He noted that A.Z. received the flu shot two weeks before the beginning of symptoms. Id. The plan was to have an infectious disease consultation and possibly have a lumbar puncture and cerebrospinal fluid ("CSF") analysis and to seek a second opinion at the Texas Children's Hospital. Id.

Infectious disease specialist Dr. Wilmer Loja evaluated A.Z. on February 20, 2017. Pet. Ex. 9 at 17-20. A.Z.'s mother reported his history. Id. at 17. Physical examination revealed A.Z. was ataxic with tremors. Id. at 19. He was "able to give three steps but with difficulty and broad base, good deep tendon reflexes, preserved sensation. [Sat] down properly and stable but not steady. Able to coordinate hands movements while seated and standing." Id. No developmental delays were noted. Id. Dr. Loja ordered extensive serology testing. Id. at 20.

On February 27, 2017, A.Z. saw pediatric neurologist Dr. Irene Patniyot at Texas Children's Hospital. Pet. Ex. 11 at 3-6. Petitioners provided A.Z.'s history, noting that since mid-January 2017, A.Z. "continued to decline in motor function." Id. At the time of the visit, it was reported that A.Z. had episodes of trembling lasting 15-20 minutes four to five times per day. Id. No associated myoclonic jerking, seizures, or other movements were reported. Id.

[23] "The CCTV/video EEG is performed to record events and to document seizure type and characteristics if any, in a very long-term recording environment with simultaneously video recording." Pet. Ex. 8 at 10.

Dr. Patniyot noted A.Z. "did receive a flu shot [two] weeks before onset of symptoms," but "[n]o varicella vaccine at that time."[24] Pet. Ex. 11 at 3. "He was sick the month prior with URI symptoms, but otherwise there were no illnesses the week prior to onset of symptoms." Id. She also noted A.Z.'s hospitalization, neurologic workup, and infectious disease consultation. Id. Petitioners reported that "a couple of viruses [] may be implicated in [A.Z.'s] current symptomology." Id.

Physical examination by Dr. Patniyot revealed mild choreiform movements of hands; low frequency, subtle intermittent head titubation; and difficulty reaching for objects. Pet. Ex. 11 at 6. A.Z. did "not cooperate" on examination of his gait but Dr. Patniyot recorded he had a "[n]ormal stance when standing up and holding [his father's] hand. Unsteady on his feet." Id. Dr. Patniyot concluded A.Z.'s symptoms were "concerning for either an acute post-infectious process or the early stages of a chronic neurodegenerative condition. Neurological work up for metabolic, heavy metal, epileptic, oncologic, and paraneoplastic etiologies ha[d] thus far been unrevealing. His cerebellar symptoms appear[ed] to be worsening, which [was] affecting his mood and ability to function." Id. The plan was to pursue further testing to identify an etiology and discuss an evaluation with a movement disorder specialist. Id.

A.Z. returned to Dr. Loja on March 1, 2017 for follow-up examination and to discuss the labs previously ordered. Pet. Ex. 9 at 23. At this visit, A.Z.'s mother reported A.Z. had diarrhea for four days but no fever. Id. Dr. Loja noted that A.Z.'s ataxia was "unchanged" since the last visit. Id. at 26. The labs taken on February 21, showed elevated serum antibodies for coxsackie virus. Id. at 26-28; see also Pet. Ex. 7 at 298-99. Dr. Loja diagnosed A.Z. with coxsackie virus infection. Pet. Ex. 9 at 26.

On March 6, 2017, A.Z. was admitted to Texas Children's Hospital where he remained until March 12. Pet. Ex. 11 at 10. Admission history was consistent with prior histories. Id. at 13. On physical examination, A.Z. had "[s]lightly increased tone in left arm . . . no spasticity noted. R[ight] hand preference . . . able to use and lift with left but prefer[ed] right." Id. at 15. Truncal ataxia was noted when A.Z. was in a seated position, and when walking, his gait was "unsteady with a wide based gait and [took] short steps." Id. Differential diagnosis was "broad for ataxia that [was] subacute in nature." Id. at 16. Acute cerebellar ataxia was a possibility, although the duration and presentation were not what would be expected. Id. OMS was also considered since it presented initially with ataxia, but it was noted that A.Z. did not have opsoclonus or myoclonus. Id. He was admitted for further evaluation and to rule out neuroblastoma. Id.

[24] Based on this entry in the records, Respondent argues that because "Dr. Patniyot referenced [A.Z.]'s prior receipt of a flu vaccine, as opposed to varicella vaccine," this "suggests a distinction being made between receipt of live attenuated versus an inactivated vaccine." Resp. Br. at 36. For further discussion, see infra Section V.A.

During this admission, A.Z. received five-days of IV steroids and one dose of rituximab,[25] which A.Z. responded to well. Pet. Ex. 11 at 42, 74, 81. He also underwent a metaiodobenzylguanidine ("MIBG")[26] scan, which was negative for neuroblastoma, and a lumbar puncture that was negative for infectious etiology.[27] Id. at 42, 71, 81, 117-27. On March 10, A.Z. was evaluated by neurologist Dr. Timothy Lotze for OMS. Id. at 74. Dr. Lotze noted a two month history of ataxia/gait imbalance, trembling, and behavioral changes, but "no prodromal infectious symptoms" and "[n]o overt opsoclonus." Id. He opined "[t]he clinical history, examination, and current response to [IV steroids] would be consistent with [OMS]." Id. The discharge diagnosis was OMS. Id. at 80. The plan was to have a steroid taper (prednisone) at home and to follow up with Dr. Lotze. Id. at 81.

A.Z. returned to Dr. Lotze on March 24, 2017 for follow-up treatment of "cryptogenic[28] [OMS]." Pet. Ex. 11 at 294. Dr. Lotze noted additional improvement in A.Z.'s symptoms since his discharge, including "recovery in his gait failure," but still had "unsteadiness in his gait and tremors in his hands." Id. Petitioners also reported A.Z. had "ongoing sleep disturbance[s]." Id. Dr. Lotze's diagnosis was "cryptogenic [OMS] with symptoms beginning in late December 2016 [and] his nadir in March 2017." Id. at 298. Dr. Lotze recorded that A.Z. "remain[ed] symptomatic" with "truncal titubation, tremor, and wide based/unsteady gait. He additionally ha[d] late insomnia with irritability. He ha[d] a premorbid language delay that was not worsened by his [OMS]." Id. The plan was for A.Z. to start speech, occupational, and physical therapy, take a second dose of rituximab, taper steroids, and start monthly intravenous immunoglobulin ("IVIG"). Id. Dr. Lotze also advised A.Z. to avoid live vaccines. Id.

A.Z. received his second dose of rituximab on April 4, 2017, and his first monthly IVIG infusion on April 28, 2017. Pet. Ex. 11 at 302, 322. He continued to receive monthly IVIG infusions through May 2018. Id. at 328-74; Pet. Ex. 12 at 1-31, 45-57.

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[25] Rituximab is "a chimeric murine/human monoclonal antibody that binds the CD 20 antigen; used as an antineoplastic in the treatment of CD20-positive, B-cell non-Hodgkin lymphoma; administered intravenously." Rituximab, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=43977 (last visited Aug. 7, 2023).

[26] MIBG is "an analogue of norepinephrine with affinity for the sympathetic nervous system and related tumors; it is believed to share the same transport pathway with norepinephrine and displace norepinephrine from intraneuronal storage granules in adrenergic nerves." Iobenguane, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=25968 (last visited Aug. 7, 2023).

[27] A.Z.'s CSF was negative for enterovirus, adenovirus, cytomegalovirus ("CMV"), varicella zoster virus ("VZV"), Epstein-Barr virus ("EBV"), human herpesviruses ("HHV") 6 and 7, and West Nile virus. Pet. Ex. 11 at 116-23.

[28] Cryptogenic means "of obscure or unknown origin." Cryptogenic, Merriam Webster Dictionary Online, https://www.merriam-webster.com/dictionary/cryptogenic (last visited Aug. 15, 2023).

On October 18, 2017, A.Z. returned to Dr. Lotze for his "cryptogenic [OMS]." Pet. Ex. 11 at 379. Dr. Lotze noted A.Z. "ha[d] done very well" since his last visit. Id. After decreasing his prednisone taper, he had "worsening of gait and increasing unsteadiness. Because of this, he was placed on dexamethasone . . . for [three] days to be given every [four] weeks alternating with his monthly IVIG infusions." Id. Since then, Petitioners reported A.Z. did "remarkably well." Id. "His gait ha[d] returned to baseline," with the exception that when he looked up, he seemed "off balance" and was "still hesitant to run." Id. "He [did] not have any eye movements or tremors," his speech had "significantly improved," he no longer had "rage attacks," and he was "sleeping through the night without medication." Id. At that time, he was not receiving any therapy. Id. He had missed his IVIG infusion that day because A.Z. had a fever. Id. Dr. Lotze documented A.Z. as having "minimal symptoms . . . with only balance issues when looking up and his current [OMS] rating scale [was] 0."[29] Id. at 383. A.Z. was to continue monthly IVIG and if he was doing well, to stop the dexamethasone and consider spacing out his IVIG infusions. Id.

At a follow-up visit with Dr. Lotze on April 11, 2018, he noted A.Z. was doing very well, "showing full remission" with "no breakthrough symptoms." Pet. Ex. 12 at 34. He had stopped the dexamethasone in November but was still doing monthly IVIG infusions. Id. Diagnosis remained "cryptogenic [OMS]" and his OMS scale score remained 0. Id. at 38. The plan was to begin tapering his IVIG infusions to six weeks and possibly stop after two additional treatments if there were no breakthrough symptoms. Id. Dr. Lotze advised A.Z. could "re-initiate vaccination [six] months after he stop[ped] the IVIG." Id.

Dr. Lotze again saw A.Z. on November 7, 2018 and documented that A.Z. completed his IVIG treatment in May. Pet. Ex. 14 at 3. A.Z. continued to have "some residual difficulties climbing stairs, pedaling and jumping with two legs" but otherwise was "doing good." Id. His neurological examination was normal, and his OMS scale score was 1 as he had "intermittent wide base gait with left leg." Id. at 5-7. Dr. Lotze "advised [Petitioners] to obtain missing vaccinations as there is no correlation with vaccines and [OMS]." Id. at 7. Petitioners were "reluctant to obtain vaccines due to concerns for a relapse." Id. A.Z. was referred to physical therapy and to have a neuropsychological evaluation. Id.

The neuropsychological evaluation was done on July 30, 2019 by Dr. Karen Evankovich at Texas Children's Hospital. Pet. Ex. 42 at 70-79. The purpose was "to assess his cognitive and behavioral functioning." Id. at 76. Dr. Evankovich noted A.Z. "demonstrated an excellent recovery from the [OMS]" and was in the average range for all the developmental assessments. Id. Speech, occupational, and physical therapy were recommended, as well as continued follow-up visits with neurology. Id. at 77.

A.Z. returned to Dr. Lotze in July 2019 and February 2020. Pet. Ex. 42 at 15-19, 33-37. A.Z. was reportedly doing very well with minimal to no signs of OMS. See id. Dr. Lotze opined

[29] For the OMS/OMA Rating Scale as referenced by Dr. Lotze, see Pet. Ex. 11 at 297.

that A.Z.'s "intermittent knee pain [did] not seem related to [OMS] or subsequent treatment."[30] Id. at 19.

No other relevant medical records were submitted.

2. Declaration of Uriel Zamora

A.Z.'s father, Mr. Zamora, executed a declaration on October 1, 2019. Pet. Ex. 1 at 6. He indicated there was no family history of neurological disorders. Id. at ¶ 2. He recalled A.Z.'s developmental condition prior to the vaccines at issue—A.Z. could pull himself up to stand and walk a few steps at 12 months. Id. at ¶ 3. At around 15 to 16 months, A.Z. "started running and walking concurrently" and was "able to go upstairs with help." Id.

Mr. Zamora noted that on November 23, 2016, "A.Z. had a runny nose and clear/green mucus [and] cough with phlegm." Pet. Ex. 1 at ¶ 6. While A.Z. presented to the doctor that day for his 18-month well-child visit, "[t]he doctor told [him] that A.Z. would not be given immunizations that day because of his illness." Id. Accordingly, they returned on November 30 and based on the doctor's physical examination, A.Z. was healthy. Id. at ¶ 7. A.Z. received the flu vaccination that day. Id. On December 14, A.Z. received the hepatitis A vaccine. Id. at ¶ 8.

"Between Christmas 2016 and New Year's Eve 2016, [Petitioners] began to notice that A.Z. had imbalance and coordination issues." Pet. Ex. 1 at ¶ 9. In early January 2017, they noticed his "symptoms increased and changed" and A.Z. had "trembling, imbalance, drooling, rage attacks, and insomnia. These symptoms began to affect A.Z.'s ability to walk." Id.

On January 7, 2017, Mr. Zamora took A.Z. to Dr. Rodriguez for a one-day history of a 102°F fever. Pet. Ex. 1 at ¶ 10. He was instructed to take A.Z. to the ED if he was not better in two days, but the fever had resolved. Id. On January 16, Mr. Zamora took A.Z. to Dr. Lopez "to report tremors." Id. at ¶ 11. He described the "episodes" and indicated A.Z.'s symptoms began three weeks prior. Id. "The doctor told [him] [A.Z.'s] diagnosis was seizures of unspecified convulsions." Id. A.Z. was taken to the hospital on January 18. Id. at ¶¶ 12-13. Petitioners reported A.Z.'s "abnormal movements [] started off intermittently" but then were observed "almost daily." Id. at ¶ 12. He recalled "A.Z. appeared awake but was not interactive during these episodes." Id. at ¶ 13. He was told the diagnosis was "myoclonic disorder." Id.

In February 2017, Mr. Zamora noted A.Z. had a neurologic exam and consultation and was given the diagnosis of ataxia. Pet. Ex. 1 at ¶¶ 14-16. After follow-up visits and another hospitalization, including five days of IV steroids and one dose of rituximab (which doctors told Mr. Zamora was to treat OMS), Mr. Zamora was told A.Z.'s final diagnosis was OMS. Id. at ¶¶ 20-23. By the end of March 2017, Mr. Zamora reported that A.Z.'s gait had improved and his other symptoms were also improving. Id. Mr. Zamora was told that A.Z.'s OMS symptoms began in late December 2016. Id. at ¶ 25.

[30] In January and February 2019, A.Z. presented to Drs. Loja and Rodriguez for fever and knee pain with swelling. See Pet. Ex. 16 at 8; Pet. Ex. 17 at 22, 27. The assessment in January was arthritis of his right knee, which was resolved by February. Pet. Ex. 17 at 25, 31.

Mr. Zamora detailed additional follow-up visits from late 2017 to early 2019 including A.Z.'s documented improvement. Pet. Ex. 1 at ¶¶ 26-30. "His speech had significantly improved" and he could say over 100 words. Id. at ¶ 26. "His gait had returned to baseline, with the exception that when he looked up it seemed that he was off balance." Id. There were "some residual issues with climbing stairs, pedaling and jumping with both legs," but he no longer had "rage attacks" or sleep problems and Mr. Zamora did not notice any tremors. Id. at ¶¶ 26, 29. Mr. Zamora continued to report that A.Z. was doing "very well" and had "minimal symptoms at home." Id. at ¶ 28.

D. Expert Reports

1. Petitioner's Expert, Dr. Marcel Kinsbourne[31]

a. Background and Qualifications

Dr. Kinsbourne is a neurologist, pediatrician, and pediatric neurologist. Pet. Ex. 20 at 1. In 1955, he obtained his B.M., B.Ch. from Oxford University Medical School, and he completed postdoctoral training through 1964 in the United Kingdom. Id.; Pet. Ex. 21 at 1. Thereafter, he obtained board certification and licensing in the United States and Canada and worked as a professor at various teaching institutions. Pet. Ex. 20 at 1; Pet. Ex. 21 at 1-2. Dr. Kinsbourne has served and is currently serving on a number of editorial boards. Pet. Ex. 21 at 3. He has authored or co-authored more than 400 publications. Id. at 5-33. Dr. Kinsbourne is no longer a practicing physician. Id. at 1-3; Pet. Ex. 20 at 1.

Dr. Kinsbourne authored the first papers and case series describing OMS and the illness was called Kinsbourne syndrome in his honor. See Pet. Ex. 29. He made significant contributions to the knowledge of OMS. Id.; Pet. Ex. 20 at 2, 11; see also Pet. Ex. 53 at 5 (explaining that since he published the earliest cases of OMS, Dr. Kinsbourne continues to be involved with colleagues who treat patients with OMS).

b. Opinion

Dr. Kinsbourne opined, more likely than not, that the flu vaccine caused A.Z.'s OMS by "up-regulating A.Z.'s immune system."[32] Pet. Ex. 20 at 13. In his second expert report, Dr. Kinsbourne opined the flu vaccine "caused or significantly contributed to the causation" of A.Z.'s OMS. Pet. Ex 45 at 5.

i. **Althen** Prong One

[31] Dr. Kinsbourne provided five expert reports. Pet. Exs. 20, 45, 50, 53, 57.

[32] Dr. Kinsbourne did not offer any opinion on the relationship, if any, between the hepatitis A vaccination and OMS.

Dr. Kinsbourne described OMS as "an autoimmune disorder, [caused by] an attack on self-antigens in the course of an immune reaction against antigens of an invading infection or of a vaccination." Pet. Ex. 20 at 10; see also Pet. Ex. 53 at 2-3. The "immune mediated attack" relevant to the cause of OMS, as described by Dr. Kinsbourne, "may involve both humeral and cellular immunity." Pet. Ex. 20 at 10.

In support of his opinions about causation, Dr. Kinsbourne relied heavily on articles authored by Dr. Michael Pranzatelli throughout his reports,[33] who, according to Dr. Kinsbourne, "has by far the most experience of OMS of anyone." Pet. Ex. 45 at 2. In his 1996 article, Dr. Pranzatelli wrote that whether OMS is "primarily a B- or T-lymphocyte problem or involves both is unclear." Pet. Ex. 31 at 8. He noted evidence for B-cell involvement included autoantibody production, and support for T-cell involvement was "T-cell infiltrate in postmortem brain, and the fact that conventional immunotherapies for OMS more effectively target T cells than B cells." Id. He concluded that an "abnormality of both humoral and cellular immunity (i.e., both B cells and T cells) is the most attractive hypothesis based on current data" for the immunological theory of OMS. Id. at 35-36. More recently, in 2017, Dr. Pranzatelli also opined that the mechanism may involve "pathological expansion" of B cells in the CSF and emphasized the role of humoral immunity. Pet. Ex. 35 at 10; see also Resp. Ex. B, Tab 8.[34]

Dr. Kinsbourne also cited studies that proposed B cell responses were implicated in the etiology of OMS. Blaes et al.[35] hypothesized that OMS "may be the result of an autoimmune process against a neuronal surface protein." Pet. Ex. 24 at 1. Acknowledging prior data showing a "predominant B-cell response in the [CSF] of children with OMS," Blaes et al. tested 14 children with OMS for "surface-binding neuronal antigens and showed that [in 10 of the 14 there were] IgG autoantibodies against the surface of cerebellar granular neurons." Id. at 1, 4. This finding supported an "autoantibody-mediated pathogenesis." Id. at 4. Although "[a]utoantibodies against surface antigens on cerebellar granular neurons have been detected in some patients, [] the specific antigens have not been identified." Pet. Ex. 26 at 2.[36]

An article by Wong[37] published in 2007, discussed more "newly identified autoantibodies, [which] include antineuroleukin, antigliadin, antendomysial, and anti-CV2. Evidence suggest[ed] that the autoantigens . . . reside in postsynaptic density, or on the cell

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[33] Dr. Kinsbourne cited five articles authored by Dr. Pranzatelli. Pet. Exs. 31-35.

[34] Michael R. Pranzatelli et al., Multifactorial Analysis of Opsoclonus-Myoclonus Syndrome Etiology ("Tumor" vs. "No Tumor") in a Cohort of 356 US Children, 65 Pediatric Blood & Cancer e27097 (2018).

[35] Franz Blaes et al., Surface-Binding Autoantibodies to Cerebellar Neurons in Opsoclonus Syndrome, 58 Annals Neurology 313 (2005).

[36] Mark P. Gorman, Update on Diagnosis, Treatment, and Prognosis in Opsoclonus-Myoclonus-Ataxia Syndrome, 22 Current Op. Pediatrics 745 (2010).

[37] Agnes Wong, An Update on Opsoclonus, 20 Current Op. Neurology 25 (2007).

surface of neurons or neuroblastoma cells . . . . Most patients, however, are seronegative for autoantibodies." Pet. Ex. 41 at 1. Similarly, Stefanowicz et al.[38] stated that "the pathogenesis of [OMS] might be an autoimmune phenomenon mediated by antibodies cross-reacting with antigens on neuroblasts and on neuronal cells in the cerebellum and the brain stem." Pet. Ex. 49 at 2.

Another paper discussed CSF B-cell expansion and/or B- and T-cell recruitment in the CSF. Pet. Ex. 26 at 2. Gorman summarized two studies reporting that OMS patients have higher CSF/serum B-cell activating factor ratios ("BAFF") as compared to controls. Id.; see also Pet. Ex. 54 at 4.[39] These studies may support the "central role of the B cell in OMS." Pet. Ex. 26 at 3. However, B cells in peripheral blood of pediatric patients with OMS has not been significantly elevated as compared to controls. Pet. Ex. 35 at 19; see also Pet. Ex. 41 at 1.

After discussing the immune-mediated mechanisms that have been described in the medical literature, Dr. Kinsbourne explained that "[i]n most cases of OMS, the immune system is overreacting to the (typically covert) presence of a neoplasm."[40] Pet. Ex. 20 at 12. While he conceded that "[t]here is no known organism, whether wild or in vaccine form, that is particularly apt to precede OMS onset," Dr. Kinsbourne opined "OMS usually starts after an infection or a vaccination." Id. at 8, 12. He posited that OMS is caused by a "challenge to the immune system by wild or vaccine viruses" that leads to a "a non-specific exacerbation of the autoimmune process." Id. at 12. "Wild and attenuated (vaccine) viruses can both cause the release of proinflammatory cytokines, notably IL-1 beta and TNF-alpha. These cytokines increase the number of antigen-presenting cells. . . . The increase in the T-cell population would have the effect of up-regulating autoimmune responses." Id. (citing Pet. Ex. 31 at 8, 16, 18-22, 36); see also Pet. Ex. 48 at 1 ("Immunizations tend to stimulate the immune system.").[41]

Dr. Kinsbourne further referenced Dr. Pranzatelli's work stating that "infectious agents such as viruses or bacteria and immunizations or vaccinations" are likely important environmental factors in developing childhood OMS. Pet. Ex. 20 at 11 (quoting Pet. Ex. 31 at 18). "In children, the immune system may become overactive because of the high frequency of viral infections." Pet. Ex. 31 at 20. "Immunizations, designed to 'boost' the immune system

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[38] Joanna Stefanowicz et al., Neuroblastoma and Opsoclonus-Myoclonus-Ataxia Syndrome – Clinical and Pathological Characteristics, 46 Folia Neuropathologica 176 (2008).

[39] Shunji Hasegawa et al., A Nationwide Survey of Opsoclonus-Myoclonus Syndrome in Japanese Children, 37 Brain & Development 656 (2015). This is also cited by Respondent. Resp. Ex. B, Tab 2.

[40] Neoplasm refers to "any new and abnormal growth; specifically, a new growth of tissue in which the growth is uncontrolled and progressive." Neoplasm, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=33438 (last visited June 27, 2023).

[41] The Immunization Fact Sheet, Nat'l Pediatric Myoclonus Ctr., https://www.omsusa.org/pranzatelli-immunization.htm (last visited July 3, 2023).

against specific antigens, which are given repetitively and overlap with the mean age of onset of OMS, initially activate T cells." Id. at 20.

But whether OMS follows infection, immunization, or is paraneoplastic, Dr. Kinsbourne opined that "the route to cerebellar injury[42] results in the same distribution of neuropathologic findings." Pet. Ex. 20 at 10. Dr. Kinsbourne noted "[t]his is not unexpected because the mechanism of antitumor or anti-viral immunity, . . . may share the same final common pathway, one that leads to an autoimmune brain disorder." Id. at 10-11 (internal quotations omitted) (quoting Pet. Ex. 31 at 20). Dr. Kinsbourne averred the "frequency of triggering by antecedent infections or vaccinations is comparable whether there is an underlying neoplasm or not." Id. at 11 (citing Pet. Ex. 28 at 1, 5).[43]

As such, Dr. Kinsbourne explained that "[p]araneoplastic OMS is strikingly similar to postviral OMS." Pet. Ex. 20 at 12. Cases of "OMS have noted viral prodromes [] even when the OMS turns out to be paraneoplastic." Id. at 11 (citing Pet. Ex. 31 at 4). Thus, in "paraneoplastic cases of OMS, antecedent non-specific virus infections are as frequently reported as they are in the 'idiopathic' cases." Id. at 12 (citing Pet. Ex. 32 at 4-5).[44] And "[i]ntercurrent virus infection cause relapses in both the idiopathic and the paraneoplastic subtypes of OMS and continue to do so after the tumor has been excised." Id. Dr. Kinsbourne concluded that the existence of a tumor does not preclude the role of infection or vaccination as a trigger for an immune challenge resulting in OMS. See id.

Dr. Kinsbourne opined on the similarities between infection and vaccination as the triggering mechanism of OMS. Pet. Ex. 20 at 12. He indicated that "the involvement of antecedent infection [in triggering OMS] is in the non-specific boost it applies to the immune system." Id.; see also Pet. Ex. 57 at 2. Thus, "[g]iven that vaccines are constructed to simulate the challenge offered the immune system by the corresponding wild-type virus," Dr. Kinsbourne opined "it should occasion no surprise that vaccinations as well as infections could initiate and/or exacerbate OMS." Pet. Ex. 53 at 3; see also Pet. Ex. 57 at 2.

Dr. Kinsbourne cited several articles that provided a list of infectious causes of OMS. Pet. Ex. 20 at 12. These include herpes viruses, varicella zoster virus ("VZV"), coxsackie virus, Epstein-Barr virus ("EBV"), *Mycoplasma pneumoniae*, hepatitis C, adenovirus C3, rotavirus, flu virus, West Nile virus, Lyme disease, streptococcus, salmonella, mycobacterium tuberculosis, and others. Id. (citing Pet. Ex. 28 at 5 tbl.2; Pet. Ex. 41 at 2; Pet. Ex. 35 at 19); Pet. Ex. 45 at 1

[42] For an explanation of the significance of OMS and the cerebellum, see Pet. Ex. 20 at 10.

[43] Stephen Hunter & Carol Kooistra, Neuropathologic Findings in Idiopathic Opsoclonus and Myoclonus, 6 J. Clinical Neuro-Ophthalmology 236 (1986).

[44] Michael R. Pranzatelli et al., Screening for Autoantibodies in Children with Opsoclonus-Myoclonus-Ataxia, 27 Pediatric Neurology 384 (2002).

(citing Pet. Ex. 46 at 4).[45] Moreover, Pranzatelli explained that in child OMS cases associated with viral illness, onset usually follows "a viral prodrome by several days, suggesting a para or postviral process." Pet. Ex. 31 at 4. Viruses, specifically neurotropic viruses, including coxsackie B, EBV, parvovirus B19, and enterovirus 71, have been identified as the antecedent viral illness. Id.; Pet. Ex. 39 at 1.

Moreover, Dr. Pranzatelli hypothesized that vaccination "may sensitize [the] immune system to [the] next presenting antigen (two-hit corollary)." Pet. Ex. 31 at 19 tbl.4. As such, he suggested that vaccines may "predispose[]" children to the illness by "general[] activation" of the immune system. Id. at 20. And in hypothesizing the immunopathophysiology of OMS, Pranzatelli warned that "[i]n children, immunization may sensitize immune system to next presenting antigen" and that "[i]mmunizations are logical candidates for costimulation in peripheral induction in children." Id. at 19 tbl.4, 20, 36. Dr. Pranzatelli noted that the mean age of onset in children was 18 months of age, a timeframe within which children receive vaccinations. Id. at 18, 36.

For additional causation support, Dr. Kinsbourne referenced case reports. He referenced his article published in 1962 which reported six cases of children with OMS. Pet. Ex. 20 at 11 (citing Pet. Ex. 29 at 1). The first child had an URI prior to and concurrent with onset; the third child had URI symptoms and a triple vaccination (diphtheria-tetanus-pertussis ("DTP") prior to onset; the fourth child had onset during a mild illness with vomiting and diarrhea; and the fifth child had onset during a mild illness with fever and rash, and one week after the poliomyelitis vaccination, experienced exacerbation of her illness. Pet. Ex. 29 at 1-4. The second and sixth children had no known antecedent infections or vaccinations. Id. This led him to hypothesize that "non-specific causes (virus infections, immunization etc.) [] set up a self-perpetuating auto-immune process." Id. at 6.

Dr. Kinsbourne next cited Stefanowicz et al., which reviewed four cases of children with neuroblastomas and OMS. Pet. Ex. 45 at 3 (citing Pet. Ex. 49 at 1). One child developed symptoms two days after receiving the measles vaccine; the child also had an URI. Pet. Ex. 49 at 2, 3 tbl.1. Another child developed symptoms after receiving a haemophilus influenzae type B vaccine. Id. at 3 tbl.1, 4. And a third child developed symptoms one month after having chicken pox. Id. at 3 tbl.1, 5. The fourth child did not have an antecedent vaccination or infection. Id. at 5-6. All of the children had neuroblastic tumors.[46] Id. at 3 tbl.1. The authors noted, "[a]n important observation in [the] group was the fact that in two of the children[,] the onset of [OMS] was primarily connected with a vaccination" supporting "proof of the immunological pathogenesis of [OMS]." Id. at 9. Stefanowicz et al. concluded that "[OMS] syndrome very rarely can [] develop in association with viral infections or vaccination." Id. at 8.

[45] John S. Tregoning & Jürgen Schwarze, Respiratory Viral Infections in Infants: Causes, Clinical Symptoms, Virology, and Immunology, 23 Clinical Microbiology Rev. 74 (2010).

[46] The first child's neuroblastic tumor was not discovered until six years after the onset of OMS. Pet. Ex. 49 at 3.

In a study by Hasegawa et al., of 23 Japanese children with OMS, 10 had associated neuroblastomas, 9 had infections, and two had associated vaccinations (flu and measles). Pet. Ex. 54 at 1, 3. McCarthy and Filiano[47] described an 11-year-old female who developed OMS 15 days after receiving her first dose of the human papillomavirus ("HPV") vaccine. Pet. Ex. 59 at 1. There was no clinical data suggesting a toxic, metabolic, infectious, immunologic, or paraneoplastic cause for her OMS. Id. Similarly, Lapenna et al.[48] described the case of a 30-year-old woman who developed OMS 15 days after a Rubella vaccination. Pet. Ex. 60 at 1. All laboratory findings were normal leading the authors to conclude the significance of "possible autoimmune post-vaccinic etiopathogenesis." Id. at 1-2.

In response to Respondent's expert, Dr. Gans, and her opinions regarding epidemiological studies, Dr. Kinsbourne pointed out that OMS is rare and "the triggering of OMS onset by any particular infection or vaccination is rarer still." Pet. Ex. 45 at 3; see also Pet. Ex. 50 at 2; Pet. Ex. 53 at 1-2. Accordingly, he opined that even robust epidemiological studies are "very unlikely to pick up a signal for such an event," which is why he believed "case reports and series are valuable in research on vaccine injury." Pet. Ex. 45 at 3.

Dr. Kinsbourne concluded there is "plentiful circumstantial evidence that vaccinations, including for [flu], can cause or trigger OMS." Pet. Ex. 50 at 3.

ii. Althen Prong Two

Dr. Kinsbourne opined it was "highly likely that the immune attack [that caused OMS] was triggered by [A.Z.'s] immune system's reaction to the [flu] vaccination." Pet. Ex. 20 at 11.

There was no evidence of neuroblastoma in A.Z.'s case. Pet. Ex. 20 at 9. While Dr. Kinsbourne initially opined that the sole cause of A.Z.'s OMS was vaccination, his position about the role of infection softened over time. In his first expert report, Dr. Kinsbourne opined that there was "no evidence . . . of any antecedent viral or bacterial infections" "documented within the applicable timeframe preceding the onset of the OMS." Id. at 9, 11. He therefore opined "[i]t [was] highly likely that [A.Z.'s] immune attack was triggered by the immune system's reaction to the [flu] vaccination." Id. at 11. Although Dr. Kinsbourne noted the flu vaccination on November 30 was "preceded by a mild untreated bronchiolitis due to an unknown organism nine days earlier," he opined there were "[n]o further symptoms of an infection [that] occurred during the weeks that led up to OMS onset." Pet. Ex. 45 at 5; see also Pet. Ex. 20 at 9.

In later reports, however, Dr. Kinsbourne acknowledged that A.Z. had "numerous viral infections of diverse kinds by diverse organisms" in the first 18 months of his life, "potentially overlapping temporally with the risk intervals of vaccinations." Pet. Ex. 45 at 1. He agreed that A.Z. was treated for bronchiolitis on November 23, 2016, one week before the flu vaccination

[47] James E. McCarthy & James Filiano, Opsoclonus Myoclonus After Human Papilloma Virus Vaccine in a Pediatric Patient, 15 Parkinsonism & Related Disorders 792 (2009).

[48] F. Lapenna et al., Post-Vaccinic Opsoclonus-Myoclonus Syndrome: A Case Report, 6 Parkinsonism & Related Disorders 241 (2000).

and about five to six weeks prior to the onset of A.Z.'s OMS. Id. However, because no specific virus was identified as the "responsible organism" for the November 23 bronchiolitis, Dr. Kinsbourne averred "[a] remote infection by an unknown organism would not preponderate as a trigger of OMS over a well-characterized vaccination." Id. at 2. He added that "[a]t most, some lingering immune stimulation" from a prior infection might have "facilitated" A.Z.'s "overreaction of the immune system to the vaccination that followed." Id. at 2.

Accordingly, Dr. Kinsbourne did not disregard the effect of a viral infection. Rather, Dr. Kinsbourne believed that even if A.Z. had a virus, the infection and the vaccination acted together to cause "a joint potentiation by an infection and a vaccination" leading to OMS. Pet. Ex. 45 at 2. In support of his opinion, he cited Piquet et al.,[49] who presented a case of a 30-year-old woman with post-vaccination OMS in the setting of a viral illness. Pet. Ex. 47 at 1. The authors concluded that "[t]he vaccination in combination with the viral illness potentiated the immune mechanism" thought to cause OMS. Id. They further noted that this conclusion was also "supported by [the patient's] recovery after receiving immunotherapy." Id. at 1-2.

While Dr. Kinsbourne opined that the vaccine and viral illness may have acted together to cause the illness, he was unable to identify any specific virus that contributed to A.Z.'s illness. Pet. Ex. 45 at 2. RSV testing on November 21, 2016, prior to both vaccines, was negative. Id. (citing Pet. Ex. 6 at 15). And he explained that the coxsackie infection was not discovered until after the onset of A.Z.'s OMS. Id. at 5. Thus, he concluded "[t]here is no way to determine when A.Z. acquired the coxsackie B virus . . . [or] whether it preceded or followed the onset of OMS and whether it was even symptomatic or only subclinical." Pet. Ex. 50 at 3.

iii. Althen Prong Three

Dr. Kinsbourne opined the onset of A.Z.'s OMS occurred 29-35 days after the flu vaccine. Pet. Ex. 45 at 2; Pet. Ex. 50 at 2. He stated this timeframe is "within the accepted risk interval of 3-42 days for autoimmune encephalopathies." Pet. Ex. 50 at 2; see also Pet. Ex. 45 at 5. Dr. Kinsbourne did not elaborate further on the risk interval beyond that it was "generally accepted in the [National Vaccine Information Center]." Pet. Ex. 45 at 5.

2. Respondent's Expert, Dr. Hayley Gans[50]

a. Background and Qualifications

Dr. Gans is board certified in pediatrics and pediatric infectious diseases. Resp. Ex. B at 1. After receiving her B.A. in biochemistry at Connecticut College and her M.D. at the State University of New York ("SUNY") Health Science Center at Syracuse, she was an intern, resident, and fellow at Stanford University School of Medicine. Resp. Ex. A at 1. She is currently a Clinical Professor in the Department of Pediatrics Division of Pediatric Infectious

[49] Amanda L. Piquet et al., Opsoclonus-Myoclonus Syndrome Post-Vaccination and Viral Illness, 3 Int'l J. Clinical Med. 304 (2012).

[50] Dr. Gans provided five expert reports. Resp. Exs. B-F.

Disease at Stanford University. Id.; Resp. Ex. B at 1. Her clinical time is spent working with children with infections and has previous clinical experience in pediatric immunology. Resp. Ex. B at 1. Dr. Gans currently does research "in the field of infectious diseases, and stud[ies] vaccine immune responses." Id. The focus of her research is "the immunologic profile in children under certain circumstances using vaccine exposure to investigate antigenic stimulation and subsequent immunity and immune competence." Id. She serves as a reviewer on several medical journals and has numerous publications. Resp. Ex. A at 4-10.

b. Opinion

Dr. Gans opined that the cause of A.Z.'s diagnosis of OMS "can be explained entirely by an infection," and thus, she concluded that there is "no causal association" between the vaccines A.Z. received and his OMS. Resp. Ex. B at 1, 10; see also Resp. Ex. C at 2 (stating that "the preponderance of evidence in A.Z.'s case is that a preceding illness led to the diagnosis of OMS, and that this alone was the cause of the OMS").

i. Althen Prong One

Dr. Gans agreed with Dr. Kinsbourne that OMS is a "rare neurologic disorder." Resp. Ex. B at 6. She also noted "[a]utoimmunity is believed to underlie paraneoplastic and nonparaneoplastic OMS in children, but specific pathogenic autoantibodies have yet to be identified." Id. at 7. However, unlike Dr. Kinsbourne, Dr. Gans opined there is no evidence supporting a causal effect between vaccination and OMS. Id.; Resp. Ex. C at 1; Resp. Ex. D at 1. Instead, Dr. Gans opined "there is strong precedent for infectious causation for OMS." Resp. Ex. B at 7. She stated, "the relationship between infections and [OMS] is well established with specific evidence revealing a causation which is not present for [flu] and hepatitis A vaccines." Id. at 1.

In support of her position that there is no association between vaccinations and OMS, Dr. Gans referred to the Vaccine Safety Datalink ("VSD"),[51] which is a "large population-based network" designed "to determine if there is a link between vaccines and a subsequent event." Resp. Ex. B at 8; see Resp. Ex. B, Tab 25.[52] She posited that VSD is the "'proven' method for conducting safety surveillance for vaccines" because it is powered to allow for "'complete capture' of events," including rare events like OMS. Resp. Ex. B at 8 (quoting Resp. Ex. B, Tab 25); see also Resp. Ex. C at 2; Resp. Ex. F at 1.

[51] The VSD Project "is a collaboration among eight medical care organizations and [the Center for Disease Control and Prevention ("CDC")], which has performed population-based research on vaccine safety in the U.S. since 1990." Resp. Ex. B, Tab 26 at 2 (Grace M. Lee et al., H1N1 and Seasonal Influenza Vaccine Safety in the Vaccine Safety Datalink Project, 41 Am. J. Preventative Med. 121 (2011)).

[52] Kevin R. Fahey, The Pioneering Role of the Vaccine Safety Datalink Project (VSD) to Advance Collaborative Research and Distributed Data Networks, 3 eGEMs, 21 (2015).

She cited a VSD study addressing the neurological outcomes of seasonal flu vaccines (one of the most studied vaccines) among 9.2 million children and adults, to opine that "no association with OMS was identified. . . . Importantly, there was no statistical signal for autoimmune neurologic diseases including GBS, demyelinating diseases, peripheral nervous system disorders, seizures, encephalomyelitis, and ataxia." Resp. Ex. B at 8 (citing Resp. Ex. B, Tab 26 at 4). Dr. Gans opined that given the large presence of ataxia in children with OMS, it "would be expected to be captured" in the study. Id.; see also Resp. Ex. F at 2. She explained that OMS is rare with a "reported incidence rate of 0.27 cases/million population in Japan and 0.8/million in the United Kingdom." Resp. Ex. E at 2 (citing Resp. Ex. B, Tab 6 at 3).[53] Given this incidence rate and the number of vaccine doses administered in the study, the "system would have been powered to find 1-3 cases of OMS." Resp. Ex. F at 2. However, she opined that ataxia was not captured and there was no association identified between OMS and flu vaccination. Id.

Dr. Gans conceded there are case reports of OMS following HPV and Rubella vaccines in teens and adults. Resp. Ex. B at 7. And while Dr. Gans agreed with Dr. Kinsbourne that "immunizations do stimulate the immune system and have been shown to temporally cause exacerbations in some autoimmune syndromes," she opined "this is not support of immunizations causing OMS." Id. at 9-10. In the large pediatric study cited by Petitioner, "[m]ore than 85% of the children had received immunizations . . . prior to onset of neurological problems." Pet. Ex. 39 at 3; see Resp. Ex. B at 7. She pointed out that Dr. Pranzatelli "recognize[d] the temporal association of children who develop OMS and childhood immunization and that studies during the diagnosis of OMS make it difficult to make a link given the delayed onset of OMS and the inciting event." Resp. Ex. B at 9; see also Resp. Ex. D at 1-2 (noting that Dr. Pranzatelli's findings are outdated and speculative). Thus, Dr. Gans opined while "[v]accines are a reasonable consideration as a trigger [for OMS] and indeed this hypothesis has been rigorously tested," they have shown "to have a negative correlation." Resp. Ex. F at 2 (emphasis omitted); see also Resp. Ex. B, Tab 8 at 8 ("The possible role of immunizations as triggers has not been discussed due to insufficient data.").

While no VSD studies have been performed with the hepatitis A vaccine, "likely because no signal has been raised," Dr. Gans noted that a post-marketing study following 80 million hepatitis A vaccine doses, showed no serious adverse events reported." Resp. Ex. B at 8 (citing Resp. Ex. B, Tab 27 at 1, 4, 7).[54] Dr. Gans opined the type of studies like VSD are "the only data that is capable of making a causal association," unlike case reports alone which can "document temporal relationships that need further evaluation." Resp. Ex. F at 2 (emphasis omitted); see also Resp. Ex. C at 2; Resp. Ex. D at 2; Resp. Ex. E at 2. "Thus, the few case reports of vaccines in teens and adults leading to OMS, are not supported by larger studies and no reports have been documented in young children." Resp. Ex. B at 8.

[53] Akshata Huddar et al., Pediatric Opsoclonus-Myoclonus-Ataxia Syndrome: Experience from a Tertiary Care University Hospital, 66 Neurology India 1332 (2018).

[54] Fuquiang Cui et al., Development, Production, and Postmarketing Surveillance of Hepatitis A Vaccines in China, 24 J. Epidemiology 169 (2014).

According to Dr. Gans, the same cannot be said about infections. Resp. Ex. F at 2. She opined that there are studies that "show the link with infections and OMS and the pathophysiology that can lead to [it]." Id. Additionally, Dr. Gans pointed out that even Dr. Pranzatelli, "who has done the largest cohort and immune studies in this area," recognized that "the role for vaccine is overshadowed by tumor and infection." Resp. Ex. E at 2. Further, Dr. Gans averred that Dr. Kinsbourne's 1962 article does not show that vaccines are associated with OMS. Resp. Ex. B at 9 (citing Pet. Ex. 29). Particularly, with regard to the third case report reviewed—the child who had URI symptoms and a vaccination prior to the onset of OMS—she opined that "the link with respiratory illness with or without vaccine receipt is the more compelling preceding event." Id.

While Dr. Gans acknowledged the "cause of OMS has not been determined,"[55] she noted "post-infectious designation is established for certain other neuroimmunologic disorders" indicating "strong precedent for infectious causation for OMS." Resp. Ex. B at 6-7; Resp. Ex. B, Tab 8 at 8; see also Resp. Ex. B, Tab 18 at 1.[56] She opined that this is especially true since "infectious pathogens have been identified" as triggers for OMS, including encephalitis virus, flu infection, EBV, *streptococcal* infection, rotavirus, and coxsackie virus. Resp. Ex. B at 6-7; see, e.g., Resp. Ex. B, Tab 11 at 1;[57] Resp. Ex. B, Tab 14 at 1.[58] She noted that coronavirus, RSV, and coxsackie are common causes for respiratory infection and "these pathogens are likely to be prominent as inciting events for children with respiratory prodromes prior to OMS." Resp. Ex. B at 8.

"Regardless of whether a specific pathogen is identified," Dr. Gans opined that "infectious prodrome is a major preceding event with respiratory illness and ear infection seen in 31 and 20%, respectively, of cases in a large pediatric population and gastrointestinal symptoms in another 20%." Resp. Ex. B at 7 (citing Pet. Ex. 39 at 3; Pet. Ex. 35 at 7). But see Resp. Ex. B, Tab 8 at 8 (finding no consistent infections among the non-tumor OMS group to suggest a uniform infectious mechanism). Dr. Gans focused on the coxsackie virus as an inciting infection for the development of OMS. Resp. Ex. B at 8.

First, she explained that the coxsackie virus infection belongs to the enterovirus family and that many disease manifestations following coxsackie virus include respiratory infections

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[55] Dr. Gans opined that "[r]egardless of the inciting event, there is a suggestion that a genetic susceptibility for OMS is at the basis of an individual's abnormal immune response to any inciting event and thus the event may not be as important as the genetic predisposition." Resp. Ex. B at 7.

[56] B. Joubert & J. Dalmau, The Role of Infections in Autoimmune Encephalitides, 175 Revue Neurologique 420 (2019).

[57] Benedikt Maria Huber et al., Mycoplasma Pneumoniae Associated Opsoclonus-Myoclonus, 169 Eur. J. Pediatrics 441 (2010).

[58] Akihiko Morita et al., Opsoclonus-Myoclonus Syndrome Following Influenza A Infection, 51 Internal Med. 2429 (2012).

and central nervous system diseases. Resp. Ex. B at 8 (citing Resp. Ex. B, Tab 28;[59] Resp. Ex. B, Tab 29).[60] Likewise, "different coxsackie virus types are [] the most common causes of infection in young children and are frequently isolated from the central nervous system." Id. Dr. Gans noted two case reports of coxsackie infection and development of OMS and concluded that "there is a causation established with one of the cases showing coxsackie isolation from the CSF." Id.

In response to Dr. Kinsbourne's opinion that "[v]accines are specifically fashioned to resemble infections" so they trigger "corresponding immune reaction," Dr. Gans opined this is not necessarily true. Pet. Ex. 57 at 2; Resp. Ex. F at 2. She stated it is a common argument in favor of the potential role of vaccines in adverse events—that if "the wild type of disease (infection with the pathogen) can cause an outcome[,] the vaccine can also cause this outcome." Resp. Ex. F at 2. But she averred it is "not necessarily true since vaccines are altered [,] and induced immunity differs when an individual is infected" and has "viral replication" as compared with "induction of immunity without [viral] replication" in the case of vaccination. Id. (citing Resp. Ex. F, Tab 1 at 1, 10-11).[61] She noted this is seen with the natural flu infection compared with the inactivated vaccine and even the live attenuated vaccine, "which more closely mimics natural disease." Id. (citing Resp. Ex. F, Tab 1 at 10-11). According to Dr. Gans, this "can be seen across vaccine types" and should be considered when comparing vaccine-induced immune responses to natural infection-induced immune responses. Id.

Accordingly, Dr. Gans concluded there is "no doubt" that there is a "negative relationship between vaccines and OMS and [a] positive link between infections and OMS." Resp. Ex. F at 2; Resp. Ex. D at 2-3. "The relationship between infections and [OMS] is well established [and] specific evidence revealing [] causation [] is not present for [flu] and hepatitis A vaccines." Resp. Ex. B at 1.

ii. Althen Prongs Two and Three

Dr. Gans noted that coronavirus, RSV, and coxsackie are common causes for respiratory infection and "these pathogens are likely to be prominent as inciting events for children with respiratory prodromes prior to OMS." Resp. Ex. B at 6, 8. She opined that instead of vaccination, A.Z.'s preceding infection triggered his OMS. Resp. Ex. E at 3.

According to Dr. Gans "[t]he data in this specific case shows a clinical syndrome and laboratory data to support preceding infection as the triggering event in A.Z.'s OMS diagnosis."

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[59] Robert C.H. Lau, Coxsackie B Virus Infections in New Zealand Patients with Cardiac and Non-Cardiac Diseases, 11 J. Med. Virology 131 (1983).

[60] Glen R. Abedi et al., Enterovirus and Parechovirus Surveillance – United States, 2014-2016, 67 MMWR Morbidity & Mortality Wkly. Rep. 515 (2018).

[61] R.J. Cox et al., Influenza Virus: Immunity and Vaccination Strategies. Comparison of the Immune Response to Inactivated and Live, Attenuated Influenza Vaccines, 59 Scandinavian J. Immunology 1 (2004).

Resp. Ex. E at 3 (emphasis omitted); Resp. Ex. F at 3 (emphasis omitted). She noted that months before receiving the vaccinations at issue, testing on January 21, 2016, revealed that A.Z. had RSV. Resp. Ex. B at 2 (citing Pet. Ex. 7 at 70). One week before the flu vaccine and approximately two weeks before the hepatitis A vaccine, A.Z. presented with an acute respiratory illness. Id. at 6. This acute respiratory illness was also present in January 2017. Id. And during his hospitalization on January 18, 2017, A.Z. tested positive for coronavirus. Id. Additional testing in February 2017 revealed elevated serum antibodies for coxsackie virus and A.Z. was diagnosed with coxsackie virus infection. Id. (citing Pet. Ex. 9 at 26).

As described above, Dr. Gans explained that respiratory illnesses/infections and viruses are "the most common preceding event in individuals who develop OMS that is not tumor induced." Resp. Ex. B at 6. She pointed out that A.Z. had "recurrent respiratory illnesses during the first 18 months of life manifesting as recurrent ear infections and lower lung infections (bronchiolitis)." Id. A.Z. had one of these "infectious episodes" with an ear infection and bronchiolitis in the fall of 2016, then once resolved, A.Z was given his vaccines. Id.

Thus, according to Dr. Gans, A.Z. "falls well in the documented cases of nonparaneoplastic OMS with an identified respiratory prodrome and ear infection, both highly associated with subsequent development of OMS, and specifically the presence of coronavirus and coxsackie virus infections." Resp. Ex. B at 7. "[T]he evidence overwhelmingly supports an infectious etiology with two diagnoses of clinical infections with bronchiolitis and ear infection [in November 2016 and January 2017] and then two infectious pathogens determined in testing, specifically coronavirus and [c]oxsackie B." Resp. Ex. F at 2. Dr. Gans concluded that "A.Z. had two known triggers for OMS, and the two vaccines that he temporally received have not been shown to cause OMS." Resp. Ex. B at 6.

Although Dr. Gans was unable to determine which infection specifically led to the development of A.Z.'s OMS, she focused on coxsackie as the trigger in A.Z.'s case. Resp. Ex. B at 7-8, 10; see Resp. Ex. C at 2. While Dr. Kinsbourne averred that coxsackie was not identified until after the diagnosis of OMS, Dr. Gans explained that "OMS is a post-infectious phenomenon," and "[i]solation of nucleic acid (i.e. PCR [test]) from a pathogen is only at time of acute infection," thus, "[a]t the time that the coxsackie was identified, it would not be expected that a PCR test would be positive since the acute infection had cleared several months prior." Resp. Ex. C at 2. Dr. Gans opined that this "is exactly why the infectious disease physician ordered antibody testing" because "information about past exposures can only be obtained through immune response to an infection, as was seen when A.Z. was tested and positive for antibodies against coxsackie virus." Id.

Dr. Gans explained that "A.Z.'s case follows this pattern beautifully: prodrome of infection and wheezing early in the course ([January 7, 2017] note) and evidence of exposure to a neurotropic pathogen at a later time." Resp. Ex. C at 2. As such, the coxsackie virus was "not subclinical or asymptomatic;" "[e]vidence of infection was shown as immune response to the virus." Id. "A.Z. had evidence of intercurrent acute illness leading to wheezing (not a symptom of OMS) at the time of visit on [January 7, 2017] when the diagnosis of OMS was initiated." Id. Thus, because when A.Z. presented with symptoms of OMS, physical examination revealed wheezing leading to the diagnosis of bronchiolitis, this "clearly [showed] an intercurrent

infection at the time." Id. She opined the identification of the infection leading to this was likely coxsackie virus infection. See id.

Dr. Gans concluded, "the preponderance of evidence in A.Z.'s case is that a preceding illness led to the diagnosis of OMS, and that this alone was the cause of the OMS." Resp. Ex. C at 2. Additionally, "the temporal administration of the [flu] and hepatitis A vaccines is not supported as the etiology or contributor to A.Z.'s illness." Resp. Ex. D at 2.

Regarding Althen prong three, Dr. Gans agreed that there was a temporal association between A.Z.'s vaccinations and the onset of his OMS. Resp. Ex. D at 2. She posited "the timing is not at question regarding the interval from immunization to OMS symptoms." Id.

IV. DISCUSSION

A. Standards for Adjudication

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" Rooks v. Sec'y of Health & Hum. Servs., 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

Petitioners' burden of proof is by a preponderance of the evidence. § 13(a)(1). The preponderance standard requires a petitioner to demonstrate that it is more likely than not that the vaccine at issue caused the injury. Moberly v. Sec'y of Health & Hum. Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Hum. Servs., 931 F.2d 867, 873 (Fed. Cir. 1991). Petitioners need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano v. Sec'y of Health & Hum. Servs., 440 F.3d 1317, 1325 (Fed. Cir. 2006). Instead, Petitioners may satisfy their burden by presenting circumstantial evidence and reliable medical opinions. Id. at 1325-26.

In particular, Petitioners must prove that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface v. Sec'y of Health & Hum. Servs., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); see also Pafford v. Sec'y of Health & Hum. Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006). The received vaccine, however, need not be the predominant cause of the injury. Shyface, 165 F.3d at 1351. A petitioner who satisfies this burden is entitled to compensation unless Respondent can prove, by a preponderance of the evidence, that the vaccinee's injury is "due to factors unrelated to the administration of the vaccine." § 13(a)(1)(B). However, if a petitioner fails to establish a prima facie case, the burden does not shift. Bradley v. Sec'y of Health & Hum. Servs., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

"Regardless of whether the burden ever shifts to the [R]espondent, the special master may consider the evidence presented by the [R]espondent in determining whether the [P]etitioner has established a prima facie case." Flores v. Sec'y of Health & Hum. Servs., 115 Fed. Cl. 157, 162-63 (2014); see also Stone v. Sec'y of Health & Hum. Servs., 676 F.3d 1373, 1379 (Fed. Cir. 2012) ("[E]vidence of other possible sources of injury can be relevant not only to the 'factors unrelated' defense, but also to whether prima facie showing has been made that the vaccine was a substantial factor in causing the injury in question."); de Bazan v. Sec'y of Health & Hum. Servs., 539 F.3d 1347, 1353 (Fed. Cir. 2008) ("The government, like any defendant, is permitted to offer evidence to demonstrate the inadequacy of the [P]etitioner's evidence on a requisite element of the [P]etitioner's case-in-chief."); Pafford, 451 F.3d at 1358-59 ("[T]he presence of multiple potential causative agents makes it difficult to attribute 'but for' causation to the vaccination. . . . [T]he Special Master properly introduced the presence of the other unrelated contemporaneous events as just as likely to have been the triggering event as the vaccinations.").

B. Causation

To receive compensation through the Program, Petitioners must prove either (1) that A.Z. suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that he received, or (2) that A.Z. suffered an injury that was actually caused by a vaccination. See §§ 11(c)(1), 13(a)(1)(A); Capizzano, 440 F.3d at 1319-20. Petitioners must show that the vaccine was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface, 165 F.3d at 1352-53).

Because Petitioners do not allege A.Z. suffered a Table Injury, they must prove a vaccine A.Z. received caused his injury. To do so, Petitioners must establish, by preponderant evidence: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen, 418 F.3d at 1278.

The causation theory must relate to the injury alleged. Petitioners must provide a sound and reliable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." Knudsen v. Sec'y of Health & Hum. Servs., 35 F.3d. 543, 548-49 (Fed. Cir. 1994). Petitioners cannot establish entitlement to compensation based solely on his assertions; rather, a vaccine claim must be supported either by medical records or by the opinion of a medical doctor. § 13(a)(1). In determining whether a petitioner is entitled to compensation, the special master shall consider all material in the record, including "any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation." § 13(b)(1)(A). The undersigned must weigh the submitted evidence and the testimony of the parties' proffered experts and rule in Petitioners' favor when the evidence weighs in their favor. See Moberly, 592 F.3d at 1325-26 ("Finders of fact are entitled—indeed, expected—to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence."); Althen, 418 F.3d at 1280 (noting that "close calls" are resolved in Petitioners' favor).

Testimony that merely expresses the possibility—not the probability—is insufficient, by itself, to substantiate a claim that such an injury occurred. See Waterman v. Sec'y of Health & Hum. Servs., 123 Fed. Cl. 564, 573-74 (2015) (denying Petitioner's motion for review and noting that a possible causal link was not sufficient to meet the preponderance standard). The Federal Circuit has made clear that the mere possibility of a link between a vaccination and a petitioner's injury is not sufficient to satisfy the preponderance standard. Moberly, 592 F.3d at 1322 (emphasizing that "proof of a 'plausible' or 'possible' causal link between the vaccine and the injury" does not equate to proof of causation by a preponderance of the evidence); Boatmon v. Sec'y of Health & Hum. Servs., 941 F.3d 1351, 1359-60 (Fed. Cir. 2019). While certainty is by no means required, a possible mechanism does not rise to the level of preponderance. Moberly, 592 F.3d at 1322; see also de Bazan, 539 F.3d at 1351.

V. CAUSATION ANALYSIS

A. Althen Prong One

Under Althen prong one, Petitioners must set forth a medical theory explaining how the received vaccine could have caused the sustained injury. Andreu, 569 F.3d at 1375; Pafford, 451 F.3d at 1355-56. Petitioners' theory of causation need not be medically or scientifically certain, but it must be informed by a "sound and reliable" medical or scientific explanation. Boatmon, 941 F.3d at 1359; see also Knudsen, 35 F.3d at 548; Veryzer v. Sec'y of Health & Hum. Servs., 98 Fed. Cl. 214, 223 (2011) (noting that special masters are bound by both § 13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If Petitioners rely upon a medical opinion to support their theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen v. Sec'y of Health & Hum. Servs., 618 F.3d 1339, 1347 (Fed. Cir. 2010) ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); Perreira v. Sec'y of Health & Hum. Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) (stating that an "expert opinion is no better than the soundness of the reasons supporting it" (citing Fehrs v. United States, 620 F.2d 255, 265 (Ct. Cl. 1980))).

The undersigned finds that Petitioners have proven by preponderant evidence that a flu vaccination can cause OMS through the immune-mediated process described by Dr. Kinsbourne for the following reasons.[62]

First and foremost, although Dr. Gans did not agree that vaccines or the flu vaccine can cause OMS, she did not take issue with the mechanistic process described by Dr. Kinsbourne, or in the articles he cited to support his theories. Although the exact cause of OMS is unknown, the current state of knowledge as described in the medical literature supports the theories advanced by Dr. Kinsbourne.

[62] The undersigned does not reach a ruling as to the hepatitis A vaccination since Dr. Kinsbourne did not offer any opinions about it.

While Dr. Kinsbourne is credited with identifying the syndrome of OMS, Dr. Pranzatelli has authored a number of articles about the pathogenesis of OMS. Dr. Pranzatelli's treatise on the immunology of OMS, published in 1996, provides a detailed discussion of humoral and cellular immunity along with the other concepts referenced by Dr. Kinsbourne. Dr. Pranzatelli also explains the role of environmental factors, including vaccinations. He concludes by stating that "[g]iven the diversity of etiologic agents in OMS . . . [and] the mechanism of anti-tumor or anti-viral immunity, however different at the outset, may share the same final common pathway, one that leads to an autoimmune brain disorder." Pet. Ex. 31 at 20. Vaccinations boost the immune system and activate the T cells (general activation). This general immune activation is followed by induction of antigens, resulting in disease specific autoantigens, molecular mechanisms or cross-reactivity (molecular mimicry), or other processes. More recently, in 2017, Dr. Pranzatelli opined that the mechanism may involve "pathological expansion" of B cells in the CSF. Pet. Ex. 35 at 10. He also emphasized the role of B cells and humoral immunity.

Wong concurs, writing that "[t]here is increasing recognition that both humoral and cell mediated immune mechanisms are involved in the pathogenesis" of OMS. Pet. Ex. 41 at 1. Wong identifies many different autoantibodies associated with OMS. Although there has been progress in identifying autoantibodies, Wong notes that most children are seronegative for antineuronal antibodies, suggesting that "a cell mediated immune response may play a role in the pathogenesis" of the illness. Id. at 2. These mechanisms are also discussed in the other medical literature. See, e.g., Pet. Ex. 54 at 4 (discussing that B cells and BAFF may play a role in the pathogenesis of OMS); Pet. Ex. 26 at 2 (same); Resp. Ex. B, Tab 3 at 4 (noting postulated mechanisms of OMS "include autoimmune response mediated by antibodies to neural antigens, and abnormal T- or B- cell activation in the CSF"); Resp. Ex. B, Tab 5 at 4 (suggesting an immune-mediated response and altered B-cell expansion in the pathophysiology of OMS); Pet. Ex. 24 at 1 (hypothesizing OMS may be the result of an "autoimmune process against a neuronal surface protein"); Pet. Ex. 49 at 2 (suggesting "the pathogenesis of OMS might be an autoimmune phenomenon mediated by antibodies cross-reacting with antigens on neuroblasts and on neuronal cells in the cerebellum and the brain stem").

Medical literature cited by both parties establishes that the pathogenesis of OMS is not fully elucidated, and more research is needed. However, the fact that the cause of OMS is not known does not defeat Petitioners' claim. Petitioners need not make a specific type of evidentiary showing or require identification of a specific trigger for an immune-mediated pathology to prove that a theory is sound and reliable by preponderant evidence. Given the state of current scientific knowledge, there is no way that a petitioner could satisfy such a requirement. And requiring proof of such would require scientific certainty, which is a bar too high. See Knudsen, 35 F.3d at 549 (explaining that "to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program").

Secondly, both experts agree that OMS is a post-infectious illness. Articles cited by both experts establish that OMS is a post-infectious condition. See, e.g., Resp. Ex. B, Tab 6 at 3 (finding a common underlying etiology of OMS is parainfections); Pet. Ex. 54 at 4 (describing that related factors of OMS include infection); Pet. Ex. 25 at 4 (stating that OMS, when not associated with a neuroblastoma, is "assumed to be postinfectious"); Pet. Ex. 39 at 2-3 (stating

that "in children without a demonstrated tumor, a viral etiology is inferred"); Pet. Ex. 31 at 4 (providing that clinically, the onset of symptoms usually follows a viral prodrome, "suggesting a para or postviral process")

In a large study of 389 children with OMS, Dr. Pranzatelli and his colleagues reported that prior to onset, upper respiratory illnesses and gastrointestinal illnesses were reported in 31% and 26% of children, respectively. Pet. Ex. 35 at 7. Most commonly reported are non-specific viral illnesses that cause URIs and infectious illnesses that cause vomiting and diarrhea. See Pet. Exs. 29, 35. But some specific pathogens include coxsackie B virus, streptococcus, EBV, mycoplasma pneumonia, Japanese encephalitis, human immunodeficiency virus, Lyme disease, and flu A infection.

Third, the medical literature also supports Dr. Kinsbourne's opinion that vaccines are causally associated with OMS. In children without a tumor, Desai and Mitchell state that the cause is "presumed to be postinfectious or postimmunization." Pet. Ex. 25 at 4. Dr. Pranzatelli wrote that vaccinations are environmental factors that cause or contribute to OMS. "Immunization, designed to 'boost' the immune system against specific antigens . . . may be another predisposing factor." Pet. Ex. 31 at 20. Vaccination was also identified as an etiology by Huddar et al. in a small study in which two of ten children received vaccinations prior to onset of OMS. See Resp. Ex. B, Tab 6 at 3, 3 tbl.1.

Most notably, in a study of 105 children, Dr. Pranzatelli and his colleagues reported that "[m]ore than 85% of the children had received immunizations (measles, mumps, rubella; [haemophilus] influenzae type B; oral polio, polio, hepatitis B, diphtheria, pertussis, including acellular pertussis, and tetanus) prior to onset of neurological problems." Pet. Ex. 39 at 3. Although the flu vaccination was not included in that study, another small study by Hasegawa et al. of 23 patients reported that a flu vaccination was administered prior to onset. Like the wide range of infections associated with OMS, there is a similarly wide range of associated vaccinations. The lack of specificity is consistent with Dr. Kinsbourne's explanation that the illness is initially triggered by general activation of the immune system.

Further, although Dr. Gans asserts that VSD is capable of complete capture of adverse events, a closer look at the methodology of the study examining the flu vaccine and adverse events, as applied to the facts of this case, shows that A.Z.'s case would have fallen outside the risk interval, and therefore, would not have been captured. In the VSD study, potential adverse events, including ataxia, were identified using ICD-9 codes[63] related to diagnoses occurring during a specified risk interval, the shortest of which was 15 days, and the longest being 42 days. See Pet. Ex. 26 at 2. A.Z. received his flu vaccine on November 30, 2017. On January 7, 2017, his diagnoses were "[u]nsteady gait, [v]ery mild motor delay, [and] [b]ronchitis." Pet. Ex. 58 at 5; Pet. Ex. 10 at 15. On January 16, 2017, his assessment was "seizures" (ICD-9 code 780.39).

[63] ICD-9 codes (the International Classification of Diseases, Ninth Revision) "is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States." International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), Ctrs. for Disease Control & Prevention: Nat'l Ctr. for Health Stats., https://www.cdc.gov/nchs/icd/icd9cm.htm (last visited Aug. 9, 2023).

Pet. Ex. 15 at 4. He was not assessed with "ataxia" (ICD-9 code 334.4) until January 18, 2017, which was 49 days after vaccination, and thus, outside the risk interval that would have captured his adverse event, given the study design. See Pet. Ex. 7 at 114. Thus, depending on the risk intervals used, the words used to describe ataxia, the clinical course of children with OMS, and the fact that diagnosis is often delayed,[64] it is not clear that the study would have captured all children with OMS.

Given the rare occurrence of OMS (calculated to be 0.03 cases per million total population in the United States),[65] and the difficulty diagnosing OMS often resulting in a delayed diagnosis, requiring that Petitioners provide more robust evidence of causation would set the bar too high. See, e.g., Knudson, 35 F.3d at 548-49; Calise v. Sec'y of Health & Hum. Servs., No. 08-865V, 2011 WL 1230155, at *27 (Fed. Cl. Spec. Mstr. Mar. 14, 2011); Coleman v. Sec'y of Health & Hum. Servs., No. 18-352V, 2021 WL 1291677, at *13-14 (Fed. Cl. Spec. Mstr. Feb. 16, 2021).

Although Dr. Gans did not specifically refute the mechanisms proffered by Dr. Kinsbourne, she did argue that epidemiology does not support an association between flu vaccination and OMS. But a lack of supportive epidemiological evidence is not dispositive. First, "epidemiological studies cannot absolutely refute a causal connection" and "cannot prove a negative. It is always possible that another epidemiological study involving a bigger population will detect an increased risk not otherwise apparent in smaller studies." Harris v. Sec'y of Health & Hum. Servs., No. 10-322V, 2014 WL 3159377, at *11 (Fed. Cl. Spec. Mstr. June 10, 2014). Additionally, "[r]equiring epidemiologic studies . . . or general acceptance in the scientific or medical communities . . . impermissibly raises a claimant's burden under the Vaccine Act and hinders the system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." Andreu, 569 F.3d at 1378 (quoting Capizzano, 440 F.3d at 1325-26); see also Althen, 418 F.3d at 1280 (noting that "close calls" are resolved in Petitioners' favor).

Lastly, there are five reasoned decisions involving vaccines and OMS. Butland v. Sec'y of Health & Hum. Servs., No. 07-111V, 2009 WL 1949059 (Fed. Cl. Spec. Mstr. June 19, 2009); Mulvaney v. Sec'y of Health & Hum. Servs., No. 05-556V, 2006 WL 2438454 (Fed. Cl. Spec. Mstr. July 26, 2006); Doe 79 v. Sec'y of Health & Hum. Servs., No. [redacted], 2010 WL 3034528 (Fed. Cl. Spec. Mstr. July 20, 2010); Tosches ex rel. Tosches v. Sec'y of Health & Hum. Servs., No. 06-192, 2008 WL 440285 (Fed. Cl. Spec. Mstr. Jan. 31, 2008); K.O. v. Sec'y of Health & Hum. Servs., No. 13-472V, 2016 WL 7634491 (Fed. Cl. Spec. Mstr. July 7, 2016).

[64] For a discussion on the delay in diagnosis of OMS, see Pet. Ex. 35 at 18; Pet. Ex. 20 at 9; Pet. Ex. 25 at 4.

[65] See Pet. Ex. 54 at 4.

In four of these cases, Dr. Kinsbourne provided an expert opinion on behalf of Petitioners,[66] with the majority resulting in finding Petitioners entitled to compensation.

In Butland, former Chief Judge and Chief Special Master Campbell-Smith awarded compensation where the evidence showed that the child had an URI when she received the measles-mumps-rubella ("MMR") and varicella vaccinations. Butland, 2009 WL 1949059, at *2, *18. The child was also later diagnosed with a ganglioneuroblastoma. Id. at *3. Dr. Kinsbourne opined that viral infections or vaccinations may act in concert with tumors to cause immunological disturbances that lead to OMS. Id. at *12. Then Special Master Campbell-Smith found that the Petitioner "presented evidence that supports a finding that viruses and vaccinations containing attenuated viruses can cause OMS," thus satisfying Althen prong one. Id. at *15.

Two cases were decided by Special Master Millman in favor of compensation. In Mulvaney, Dr. Kinsbourne also relied heavily on articles and opinions by Dr. Pranzatelli, offering opinions about the causal mechanisms proffered here. Mulvaney, 2006 WL 2438454, at *11-13; see also Doe 79, 2010 WL 3034528, at *11-12.

In a fourth case, Tosches, Petitioner alleged that the diphtheria-tetanus-acellular pertussis ("DTaP") vaccine caused his son to develop OMS due to "an aberrant immune system response, either bystander activation or epitope spreading." Tosches, 2008 WL 440285, at *13. Although Special Master Moran did not grant entitlement to compensation, he found that the Respondent's expert "did not challenge the proposition that immunization could play a role in causing OMS." Id. Thus, Special Master Moran found that Petitioner met his burden of proof as to Althen prong one.[67] Id.

While the facts in the above cases are distinguishable from the present case, Dr. Kinsbourne's opinions—in which he offered the same theory as here—were found to establish preponderant evidence of causation as to Althen prong one. Although decisions of other special masters are not binding, the undersigned generally agrees with the reasoning of her colleagues in these cases as to Althen prong one, and further acknowledges that they provide additional support in favor of Petitioners here as to Althen prong one. See Boatmon, 941 F.3d at 1358; Hanlon v. Sec'y of Health & Hum. Servs., 40 Fed. Cl. 625, 630 (1998), aff'd, 191 F.3d 1344 (Fed. Cir. 1999).

[66] A different expert testified on behalf of Petitioner in the fifth case. K.O., 2016 WL 7634491, at *2. Special Master Moran found that the proffered theory of molecular mimicry was "far too general to be persuasive." Id. at *1. Further, onset occurred outside the time frame that the experts agreed was medically acceptable. Id. For these reasons, Special Master Moran denied compensation. Id. at *1, *20.

[67] Based in part on another expert's testimony, Special Master Moran found the Petitioner failed to meet his burden as to Althen prong two, because the child had received three prior DTaP vaccinations without an adverse reaction and the treating physicians did not support causation. Tosches, 2008 WL 440285, at *3-4, *8, *13-15.

For the reasons described above, the undersigned finds that Petitioners have proven that the immune-mediated theories proffered are sound and reliable by preponderant evidence and therefore, have satisfied their burden as to Althen prong one.

B. Althen Prong Two

Under Althen prong two, Petitioners must prove by a preponderance of the evidence that there is a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." Capizzano, 440 F.3d at 1324 (quoting Althen, 418 F.3d at 1278). "Petitioner[s] must show that the vaccine was the 'but for' cause of the harm . . . or in other words, that the vaccine was the 'reason for the injury.'" Pafford, 451 F.3d at 1356 (internal citations omitted).

The undersigned finds that Petitioners have proven prong two by preponderant evidence for three reasons: (1) A.Z.'s clinical course is consistent with post-infectious and post-vaccination OMS, (2) A.Z.'s illness responded to immune modulating therapy, and (3) Dr. Kinsbourne's opinion that concurrent causes may work together to boost the immune system is supported by medical literature evidence.

A brief overview of A.Z.'s medical records show that on November 21, 2016, he had acute bilateral otitis media and acute bronchiolitis. On November 23, 2016, his cough was worse. On November 30, he received the flu vaccination, followed by the hepatitis vaccination on December 14, 2016. On January 7, 2017, A.Z.'s gait had been unsteady for four days. A.Z. was hospitalized on January 18, 2017, and lab work drawn that day revealed he was positive for coronavirus. On January 18, 2017, A.Z. was diagnosed with ataxia. A follow-up evaluation and testing by infectious diseases on February 20, 2017 revealed that A.Z. had positive coxsackie antibody titers, and he was diagnosed with coxsackie virus infection. After hospitalization and consultation by experts, and diagnostic studies, A.Z. was diagnosed with OMS on March 10, 2017.

Dr. Kinsbourne opined that even if A.Z. had a viral infection, it and the vaccine acted together to jointly induce the immune system, leading to OMS. He cited Piquet et al., who reported the case of a 30-year-old woman with post-vaccination OMS in the setting of a viral illness. Piquet et al. concluded that both vaccination and viral infection "potentiated the immune mechanism" that caused OMS. Pet. Ex. 47 at 1. They also noted that after receiving immunotherapy, the patient recovered, and this fact supported the theory that OMS was caused by both vaccination and infection.

This opinion that "[s]everal factors may contribute to the sequence of events leading to immune system dysregulation in OMS" was also embraced by Dr. Pranzatelli. Pet. Ex. 31 at 20. He noted that a child's immune system may "become overactive because of the high frequency of viral infections, which average 10 or more yearly during infancy." Id. The medical literature shows that a wide range of infections have been causally associated with OMS, including coxsackie virus. See, e.g., Pet. Ex. 39 at 1-2; Resp. Ex. B, Tab 3 at 4. In this context, Dr. Pranzatelli describes vaccinations as "another predisposing factor" that causes a "boost" of the immune system resulting in activation of T cells. Pet. Ex. 31 at 20. Moreover, Pranzatelli and

his colleagues reported that more than 85% of children in their study had received vaccinations prior to the onset of OMS.

Further, case reports describe histories that include both infection and vaccination prior to onset of OMS. For example, in Dr. Kinsbourne's case series, one of the six children had an upper respiration illness and received a vaccination prior to onset. Pet. Ex. 29 at 1. Similarly, Stefanowicz et al. reported a child who had an infection of the upper respiratory tract and vaccination prior to developing symptoms. Pet. Ex. 49 at 2, 3 tbl.1.

The combined effect of virus, vaccination, and neuroblastoma in causing OMS was addressed in Butland. In that case, the child had an URI at the time that she received the MMR and varicella vaccinations. Butland, 2009 WL 1949059, at *16. There, Dr. Kinsbourne testified that the vaccinations further "up-regulated" the immune system, and therefore, they substantially contributed to her OMS. Id. Then Special Master Campbell-Smith rejected the Respondent's position that the child's neuroblastoma was the sole cause of OMS and found Dr. Kinsbourne's opinion as to combined causes to be more persuasive. Id. at *16-17.

In Mulvaney, the child had a history of several viral illnesses and had a neuroblastoma when he received the MMR vaccination, and "within a medically appropriate time frame, he began to manifest signs of OMS." Mulvaney, 2006 WL 2438454, at *12. Special Master Millman noted that in Shyface, "the Federal Circuit emphasized that the vaccine does not have to be the predominant factor in order for [P]etitioners to prevail." Id. (citing Shyface, 165 F.3d at 1353). Shyface instructs that proof of a substantial factor satisfies the requirements of the Vaccine Act. Shyface, 165 F.3d at 1353 (finding that "although the [Petitioners] did not prove the [] vaccine was the only or predominate cause of his death, the requirements of the Vaccine Act are met prima facie upon proof of the substantial factor criterion").

Where there are two potential causes for an illness, a petitioner is not required to eliminate the other potential cause in order to be entitled to compensation. Walther v. Sec'y of Health & Hum. Servs., 485 F.3d 1146, 1149-52 (Fed. Cir. 2007) (ruling "[P]etitioner does not bear the burden of eliminating alternative independent potential causes"); Pafford, 451 F.3d at 1358-59. Moreover, case law instructs that where two causes combine to cause a vaccine-related illness, and it is not possible to determine which of the causes was most responsible, it is appropriate to find in favor of compensation. See, e.g., Althen, 418 F.3d at 1280 (noting that "close calls" are resolved in Petitioners' favor); Shyface, 165 F.3d at 1352-53 (finding in favor of Petitioners where both a vaccine and an *Escherichia coli* infection contributed to the death because "concurrent forces may bring about a single harm" (emphasis omitted) (internal quotations omitted)).

Dr. Gans argues that A.Z.'s infection alone was sufficient to cause OMS, and the sole cause of his OMS. But she cites no medical treatise or other evidence to support her opinion that in the face of two potential causes, both of which have been causally associated with the vaccine-related illness, it is reasonable to reject one of the causes. Moreover, the medical literature does not advance such a theory. As described above, Dr. Pranzatelli opined that in OMS, "several factors" may contribute" to "immune dysregulation." Pet. Ex. 31 at 20. Here, those factors include both viral infection and vaccination. Therefore, the undersigned finds that the flu

vaccination received by A.Z. was a substantial contributing factor to his immune system dysregulation, and as contemplated by Shyface, this finding weighs in favor of Petitioners as to Althen prong two.

Next, in Dr. Pranzatelli's 1996 paper on the mechanism of OMS, he opines that although OMS does not meet the five classic criteria[68] to conclude that it is an autoimmune illness, there is "circumstantial evidence" that "supports an autoimmune basis for OMS." Pet. Ex. 31 at 2. One of the pieces of circumstantial evidence described by Dr. Pranzatelli included a patient's favorable response to immune modulating therapy. Id. at 26-32. A.Z. was treated successfully with dexamethasone, IVIG, and rituximab. Dr. Kinsbourne opines that since receiving these therapies, A.Z. had done "remarkably well per his family." Pet. Ex. 20 at 6. The fact that A.Z. responded well to immunomodulating therapy provides circumstantial evidence that his antecedent infection and vaccination caused an autoimmune illness, OMS.

Third, in determining whether Petitioners have put forth preponderant evidence of Althen prong two, the undersigned generally takes into consideration the opinions of the treating physicians. Treating physician statements are typically "favored" as treating physicians "are likely to be in the best position to determine whether a 'logical sequence of cause-and-effect show[s] that the vaccination was the reason for the injury.'" Capizzano, 440 F.3d at 1326 (quoting Althen, 418 F.3d at 1280). However, no treating physician's views bind the special master, per se; rather, their views are carefully considered and evaluated. § 13(b)(1); Snyder v. Sec'y of Health & Hum. Servs., 88 Fed. Cl. 706, 746 n.67 (2009). "As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases." Welch v. Sec'y of Health & Hum. Servs., No. 18-494V, 2019 WL 3494360, at *8 (Fed. Cl. Spec. Mstr. July 2, 2019).

Here, there are several references in A.Z.'s medical records by his treating physicians relevant to vaccine causation. On February 14, 2017, Dr. Garcia questioned the possibility of a post-immunization reaction. He stated, "the possibility of postimmunization reaction is strongly considered" and noted the prior flu vaccination. Pet. Ex. 8 at 12. Dr. Garcia did not, however, provide the basis of his opinion, or explain why he strongly considered a post-immunization reaction. On November 6, 2018, Dr. Lotze recommended that Petitioners have A.Z.'s vaccinations brought up to date. A.Z.'s parents were concerned that he might have a relapse. In response, Dr. Lotze noted "there is no correlation with vaccines and [OMS]." Pet. Ex. 14 at 7. Dr. Lotze did not provide the reasons for his opinion that there is no correlation between A.Z.'s

[68] OMS fails the first criterion (a "defined circulating antibody or cell-mediated immunity to autoantigens") because most OMS patients do not have detectable levels of antibodies. Pet. Ex. 31 at 2. OMS fails the second criterion (requiring a "specific autoantigen") because it is unknown. Id. And the last three criteria require studies (which are not available here) inducing disease by passive antibody transfer in an animal model, inducing disease in an animal model using an immunization made with the self-antigen and Freund's adjuvant, and which must generate autoantibodies. Id.

vaccinations and his OMS.[69] Lastly, on February 27, 2017, Dr. Patniyot noted that A.Z. received the flu shot two weeks before onset and that he had an URI the month before onset. Pet. Ex. 11 at 3.

As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases." Welch v. Sec'y of Health & Hum. Servs., No. 18-494V, 2019 WL 3494360, at *8 (Fed. Cl. Spec. Mstr. July 2, 2019). An opinion by a treating physician that is not supported by a factual basis or other evidence is conclusory in nature. And a "treating physician's recognition of a temporal relationship does not advance the analysis of causation." Isaac v. Sec'y of Health & Hum. Servs., No. 08-601V, 2012 WL 3609993, at *26 (Fed. Cl. Spec. Mstr. July 30, 2012); see also Robertson v. Sec'y of Health & Hum. Servs., No. 18-554V, 2022 WL 17484980, at *17 (Fed. Cl. Spec. Mstr. Dec. 7, 2022) (finding treating physicians' statements of mere suspicion fall short of an opinion supporting vaccine causation); Cedillo v. Sec'y of Health & Hum. Servs., 617 F.3d 1328, 1347 (Fed. Cir. 2010) (concluding the special master did not err in affording little weight to the opinions of Petitioner's treating physicians where "none of the treating physicians concluded that the [] vaccine caused [Petitioner's] [condition]").

Because the references to vaccination by Dr. Garcia and Dr. Lotze do not provide any supporting facts or foundation, and because Dr. Patniyot's reference notes only a temporal association between vaccination and the onset of A.Z.'s OMS, the undersigned does not afford significant weight to them.

Instead, the undersigned relies upon the expert opinions, medical records, and medical literature and finds that Petitioners have provided preponderant evidence of a logical sequence of cause and effect, and have satisfied the criteria of Althen prong two.

C. Althen Prong Three

Althen prong three requires Petitioners to establish a "proximate temporal relationship" between the vaccination and the injury alleged. Althen, 418 F.3d at 1281. That term has been defined as a "medically acceptable temporal relationship." Id. Petitioners must offer "preponderant proof that the onset of symptoms occurred within a time frame for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." de Bazan, 539 F.3d at 1352. The explanation for what is a medically acceptable time frame must also coincide with the theory of how the relevant vaccine can cause the injury alleged (under Althen prong one). Id.; Koehn v. Sec'y of Health & Hum. Servs., 773 F.3d 1239, 1243 (Fed. Cir. 2014); Shapiro, 101 Fed. Cl. at 542; see also Pafford, 451 F.3d at 1358. A temporal relationship between a vaccine and an injury, standing alone, does not constitute preponderant evidence of vaccine causation. See, e.g., Veryzer, 100 Fed. Cl. at 356

[69] Dr. Kinsbourne responded to Dr. Lotze's note by referring to Dr. Pranzatelli who "emphatically disagrees with resuming vaccinations after the onset of OMS." Pet. Ex. 45 at 2-3 (citing Pet. Ex. 48). Once a child is off all immunotherapy for at least two years, some vaccines can be resumed, but see the caveats provided. Pet. Ex. 48 at 1.

(explaining that "a temporal relationship alone will not demonstrate the requisite causal link and that [P]etitioner must posit a medical theory causally connecting the vaccine and injury").

Dr. Kinsbourne opined the onset of A.Z.'s OMS occurred 29-35 days after the flu vaccine,[70] within the risk interval of 3-42 days that for this type of autoimmune illness. Dr. Gans agreed that there was a temporal association between A.Z.'s vaccinations and the onset of his OMS.

In the case reports of OMS, onset occurred within 3 to 42 days of vaccination and/or infection. For example, Dr. Kinsbourne reported that onset occurred one month after cough and vaccination. See Pet. Ex. 29 at 2. Morita et al. reported onset one week after diagnosis with flu infection. Huber et al. reported pneumonia two weeks before onset, febrile respiratory illness four weeks prior to onset, and febrile infection with sore throat and cough two weeks before onset.

Since the experts agree that a temporal association exists between vaccination and onset of A.Z.'s OMS, and this time frame is supported by medical literature as appropriate given the immune-mediated mechanisms, the undersigned finds that Petitioners have proven Althen prong three by preponderant evidence.

D. Alternative Causation

Because the undersigned concludes that Petitioners have established a prima facie case, Petitioners are entitled to compensation unless Respondent can put forth preponderant evidence "that [Petitioner's] injury was in fact caused by factors unrelated to the vaccine." Whitecotton v. Sec'y of Health & Hum. Servs., 17 F.3d 374, 376 (Fed. Cir. 1994), rev'd on other grounds sub nom., Shalala v. Whitecotton, 514 U.S. 268 (1995); see also Walther, 485 F.3d at 1151. The undersigned agrees with Respondent's expert there is evidence that A.Z. had an antecedent or concurrent infection prior to the onset of OMS, but as described above, the undersigned finds that the vaccination was a significant contributing factor.

Moreover, because the infection was not the sole factor, Respondent cannot prevail on this argument. de Bazan, 539 F.3d at 1354 (holding that Respondent's burden is to "identify[ ] a particular [unrelated] factor (or factors) and present[] sufficient evidence to establish that it was the sole substantial factor in bringing about the injury," thus "excluding the vaccine as a substantial factor"); Deribeaux ex rel. Deribeaux v. Sec'y of Health & Hum. Servs., 105 Fed. Cl. 583, 595 (2012), aff'd, 717 F.3d 1363 (Fed. Cir. 2013); Stone v. Sec'y of Health & Hum. Servs., 95 Fed. Cl. 233, 237 (2010).

VI. CONCLUSION

[70] A.Z. received his flu vaccination on November 30, 2016, and onset of his gait ataxia was January 3, 2017. Thus, the undersigned finds onset to be approximately 34 days after vaccination, consistent with Dr. Kinsbourne's opinion.

For the reasons discussed above, the undersigned finds that Petitioners have established by preponderant evidence that A.Z.'s flu vaccination significantly caused or contributed to A.Z.'s condition. Therefore, Petitioners are entitled to compensation. A separate damages order will issue.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Special Master